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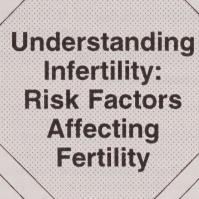
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UNDERSTANDING INFERTILITY: Risk Factors Affecting Fertility

Research Studies of the Royal Commission on New Reproductive Technologies





Volume 7 of the Research Studies

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Preface from the Chairperson



As Canadians living in the last decade of the twentieth century, we face unprecedented choices about procreation. Our responses to those choices — as individuals and as a society — say much about what we value and what our priorities are. Some technologies, such as those for assisted reproduction, are unlikely to become a common means of having a family — although the number of children born as a result of these techniques is greater than the number of infants placed for adoption in Canada. Others, such as ultrasound during pregnancy, are already generally accepted, and half of all pregnant women aged 35 and over undergo prenatal diagnostic procedures. Still other technologies, such as fetal tissue research, have little to do with reproduction as such, but may be of benefit to people suffering from diseases such as Parkinson's; they raise important ethical issues in the use and handling of reproductive tissues.

It is clear that opportunities for technological intervention raise issues that affect all of society; in addition, access to the technologies depends on the existence of public structures and policies to provide them. The values and priorities of society, as expressed through its institutions, laws, and funding arrangements, will affect individual options and choices.

As Canadians became more aware of these technologies throughout the 1980s, there was a growing awareness that there was an unacceptably large gap between the rapid pace of technological change and the policy development needed to guide decisions about whether and how to use such powerful technologies. There was also a realization of how little reliable information was available to make the needed policy decisions. In addition, many of the attitudes and assumptions underlying the way in which technologies were being developed and made available did not reflect the profound changes that have been transforming Canada in recent decades. Individual cases were being dealt with in isolation, and often in the absence of informed social consensus. At the same time, Canadians were looking

more critically at the role of science and technology in their lives in general, becoming more aware of their limited capacity to solve society's problems.

These concerns came together in the creation of the Royal Commission on New Reproductive Technologies. The Commission was established by the federal government in October 1989, with a wide-ranging and complex mandate. It is important to understand that the Commission was asked to consider the technologies' impact not only on society, but also on specific groups in society, particularly women and children. It was asked to consider not only the technologies' scientific and medical aspects, but also their ethical, legal, social, economic, and health implications. Its mandate was extensive, as it was directed to examine not only current developments in the area of new reproductive technologies, but also potential ones; not only techniques related to assisted conception, but also those of prenatal diagnosis; not only the condition of infertility, but also its causes and prevention; not only applications of technology, but also research, particularly embryo and fetal tissue research.

The appointment of a Royal Commission provided an opportunity to collect much-needed information, to foster public awareness and public debate, and to provide a principled framework for Canadian public policy on the use or restriction of these technologies.

The Commission set three broad goals for its work: to provide direction for public policy by making sound, practical, and principled recommendations; to leave a legacy of increased knowledge to benefit Canadian and international experience with new reproductive technologies; and to enhance public awareness and understanding of the issues surrounding new reproductive technologies to facilitate public participation in determining the future of the technologies and their place in Canadian society.

To fulfil these goals, the Commission held extensive public consultations, including private sessions for people with personal experiences of the technologies that they did not want to discuss in a public forum, and it developed an interdisciplinary research program to ensure that its recommendations would be informed by rigorous and wide-ranging research. In fact, the Commission published some of that research in advance of the Final Report to assist those working in the field of reproductive health and new reproductive technologies and to help inform the public.

The results of the research program are presented in these volumes. In all, the Commission developed and gathered an enormous body of information and analysis on which to base its recommendations, much of it available in Canada for the first time. This solid base of research findings helped to clarify the issues and produce practical and useful recommendations based on reliable data about the reality of the situation, not on speculation.

The Commission sought the involvement of the most qualified researchers to help develop its research projects. In total, more than 300

scholars and academics representing more than 70 disciplines — including the social sciences, humanities, medicine, genetics, life sciences, law, ethics, philosophy, and theology — at some 21 Canadian universities and 13 hospitals, clinics, and other institutions were involved in the research program.

The Commission was committed to a research process with high standards and a protocol that included internal and external peer review for content and methodology, first at the design stage and later at the report stage. Authors were asked to respond to these reviews, and the process resulted in the achievement of a high standard of work. The protocol was completed before the publication of the studies in this series of research volumes. Researchers using human subjects were required to comply with appropriate ethical review standards.

These volumes of research studies reflect the Commission's wide mandate. We believe the findings and analysis contained in these volumes will be useful for many people, both in this country and elsewhere.

Along with the other Commissioners, I would like to take this opportunity to extend my appreciation and thanks to the researchers and external reviewers who have given tremendous amounts of time and thought to the Commission. I would also like to acknowledge the entire Commission staff for their hard work, dedication, and commitment over the life of the Commission. Finally, I would like to thank the more than 40 000 Canadians who were involved in the many facets of the Commission's work. Their contribution has been invaluable.

Patricia a. baird

Patricia Baird, M.D., C.M., FRCPC, F.C.C.M.G.



Introduction



The direct "causes" of infertility are, in many cases, relatively clear — blocked fallopian tubes, ovulatory problems, low sperm counts. What is less obvious is the sequence of events leading to those particular conditions — and this information needs to be understood in order for infertility to be effectively prevented.

The risk factors that may lead to conditions causing infertility are the subject of this volume. In Volume 6, we learned that 7 percent of couples of reproductive age in Canada are infertile — they have not had a pregnancy even though they have not been using contraception and have been cohabiting for two years. This volume sheds some light on the circumstances that may lead to this situation. The better understanding of risk factors that emerges from this volume provides the basis for the next volume in this series, which focusses on the prevention of infertility.

There are three important aspects of risk factors that must be taken into account and that make them particularly difficult to analyze. The first is that they may affect an individual's fertility at different stages of life and in various settings, perhaps years before any attempt to have a family. The second is that they are remarkably diverse and may interact with each other, and that knowledge about them extends into broader areas of biomedical, sociological, and other fields of research. The third aspect is that, when two people try to have a family, each brings his or her own history of exposure to risk factors.

Given these factors, the Commission knew it was unlikely that definitive answers about the causes of infertility could be provided at this time. Commissioners therefore chose to take a global approach to the issue, commissioning research studies that would discover as much as possible about factors identified as posing possible risks to fertility. At the same time, the Commission encouraged the integration of research from different academic and medical disciplines.

The risk factors that have been identified can be grouped into three broad categories. The first includes factors such as sexually transmitted diseases (STDs), delayed childbearing, drug or alcohol use, eating disorders, and excessive exercise, which can be defined as "personal" risk factors. The second category incorporates risk factors that are medically based—the use of various methods of contraception, endometriosis, and medical interventions. The third category includes those risk factors that are related to exposure to occupational and environmental hazards. While all these risk factors play a role in creating conditions that may lead to infertility, some are more significant than others, either because of the numbers of people exposed to them or because they are particularly harmful in nature.

The Studies

In their overview of the links between STDs and infertility, Allan Ronald and Rosanna Peeling make the points that STDs may affect as many as one in five Canadians during their sexually active years, that they are difficult to detect, and that they cause between 15 and 20 percent of all infertility in Canada. The authors outline how STDs may lead to tubal infertility, ectopic pregnancies, and, to a lesser degree, spontaneous abortions, stillbirths, premature labour, and neonatal infections. STDs are most common in young people, who are also the group most sexually active. This means that young men and women may be placing their future fertility at risk without realizing the consequences. STDs are preventable, however, and, on the positive side, Drs. Ronald and Peeling believe that most of the components of an effective prevention program are already in place in Canada. Effective leadership is required, though, at the federal and provincial levels to make this a reality.

As Joan Jantz-Lee makes clear in her review of the effects of aging on fertility, fertility in women decreases after age 30, and particularly after age 35. This decline in fertility is partly inevitable, the result of the biological aging of the reproductive system. It is also, in some women, the result of the accumulated impact of years of exposure to other risk factors. The finding that for women the time needed to conceive increases, especially from the late thirties on, is important information both for couples deciding when to start trying to conceive and for physicians trying to find a balance between waiting an appropriate length of time for conception to occur naturally and referring patients to fertility programs for treatment.

Unlike decreases in fertility due to aging, decreases in fertility that may result from the use of tobacco, alcohol, and caffeine are reversible. In her study of the effects of licit and illicit drugs on fertility, Hélène Boyer finds that there are clear threats to both male and female fertility from drugs. For instance, smoking not only can reduce the birthweight of infants, but also is associated with delays in conception. There is still much to be learned, however, about the precise relationship between

various drugs, both legal and illegal, and infertility. For instance, the effects of caffeine — the most frequently consumed legal drug in the world — are still unclear. Research is needed to understand the effects of various combinations of drugs, since, for example, smokers also tend to be consumers of alcohol and caffeine. Dr. Boyer concludes that the effects of most drugs, licit or illicit, on fertility and on the fetus are numerous "and argue in favour of prudence and moderation."

The risk factors examined by Sarah Maddocks — weight, eating behaviours, and exercise — are similar to those reviewed by Dr. Boyer in that they are reversible and related to personal behaviours. Infertility appears to be associated with having either too much body fat (as with obesity) or too little (as with excessive exercise, eating disorders, or being underweight). There is evidence that fertility can be restored with proper diet, correct body weight, and not exercising to excess. Dr. Maddocks calls attention, however, to the need for more information on the biopsychological factors underlying these conditions.

The examination of the role of medical factors in infertility begins with a look at contraception. Norman Barwin and William Fisher identify two kinds of concerns. The first concern is that there may be unintended effects on fertility associated with some methods of contraception, the bestknown example being the relationship between the use of some intrauterine devices (IUDs) and pelvic inflammatory disease with consequent tubal damage. The second concern is that the inability of oral contraceptives to protect against STDs may not be taken into account when a woman who has more than one sexual partner, or whose partner has had other partners, chooses a method of contraception. Drs. Barwin and Fisher document what is known about the former concern, but see the latter concern as posing the greater threat to fertility. They identify a need to ensure that both fertility control and infertility prevention are considered by women choosing a method of contraception, and they call for educational efforts to inform women about the need to make a choice with both goals in mind. In this way, they say, appropriate choice of contraception can play an important role in protecting rather than endangering fertility.

Endometriosis is a condition seen in many women in their childbearing years. It involves endometrial tissue appearing outside the womb, in the pelvic cavity or elsewhere. It is perhaps the most common condition seen by gynaecologists, but, as Arlyss Ponchuk points out, neither its cause nor its cure is known. Moderate or severe endometriosis is clearly associated with infertility, but the relationship between minimal or mild endometriosis and infertility is, as yet, unclear, as many women with mild endometriosis do not have difficulty having children. Ms. Ponchuk raises the possibility that a relationship between endometriosis and infertility may not be one of cause and effect, but that an as-yet-unknown third factor may cause infertility in women with endometriosis, and she calls for more research in this area.

Infertility can be an intended or unintended consequence of medical intervention or treatment. Infertility may be desired, as in the case of contraceptive use or after a tubal ligation or vasectomy. In some cases, medical intervention may be necessary and the resulting infertility anticipated — for example, after a hysterectomy. Much less frequently, infertility may be an unintended side-effect of a diagnostic or treatment procedure. Sylvie Dumas, Édith Guilbert, and Jacques Rioux provide a comprehensive survey of the risk of the potentially negative effect on fertility of a wide range of diagnostic and therapeutic procedures. They draw attention to the frequency of voluntary sterilization. They also outline the known risk that fertility may not be restored in individuals having reversals of these sterilization procedures. They note that this has obvious ethical implications for physicians counselling individuals about voluntary sterilization, who must ensure that the individuals concerned understand and consider that the effects of the sterilization cannot reliably be reversed.

The next two studies, taken together, provide a useful introduction to the broad spectrum of issues relating to environmental and occupational threats to fertility. They show the complex nature of exposure to these hazards and outline how this complexity can be addressed in order to advance knowledge in these areas. More information is needed to support enlightened policies and programs aimed at preventing infertility resulting

from such exposure.

Patabendi Abeytunga and Maritza Tennassee focus on record linkage as a technique that can be applied to questions relating to reproductive health in the same way as it has been used in other areas of occupational health. They outline the range of exposures that could have an effect on the human reproductive process. They identify Canadian data bases on exposures and health outcomes that could be linked to provide needed information in this area. This study, together with the two papers on record linkage in Volume 11, makes a compelling case for the better use of existing data in this country to provide valuable information for preventing and treating infertility.

John Jarrell, Judy Seidel, and Philip Bigelow take two approaches to an assessment of the possible effects of one particular chemical agent, hexachlorobenzene (HCB), on fertility. First, they use meta-analysis (which is explained in greater detail in Volume 11) to examine all relevant scientific literature on this chemical agent. The results of this review are inconclusive: it is clear that in high concentrations this chemical causes disease and perinatal loss, but its effect at usual levels of exposure is unknown. The authors note that this question is important and requires further study. To supplement this analysis, the authors conducted a study examining the presence of certain chemical agents in the follicular fluid of women in Canada who had had *in vitro* fertilization (IVF). It is not possible to draw firm conclusions from this small study, as they are complicated by the fact that lower levels of HCB found in women who had had children may have been the result of the HCB being distributed into fetal tissues.

However, Dr. Jarrell and his colleagues have established a useful source of data for future research on HCB and the risk it poses to fertility. They have demonstrated how different research methodologies can be used to attempt an elucidation of environmental risks to fertility. They call for continued monitoring of the follicular fluid of women receiving IVF for what they call "priority chemicals" — chemicals thought to be a risk to either female or male fertility — to build on the information they have collected in this study.

The pilot study by Peggy Millson on determining the relative importance of risk factors for infertility is an important attempt to synthesize information and to draw useful conclusions that may guide action. It examines whether it is possible, with the currently available information about risk factors for infertility, to come to an assessment that is useful in guiding policy and establishing priorities about prevention. She considers the frequency of known risk factors, what is known about their effect, and whether they are preventable. She concludes that STDs should be ranked highest in prevention efforts, but that tobacco use by women and alcohol use by both sexes should also be ranked high. She notes that it is essential that better information regarding occupational and environmental exposures and outcomes be collected.

The author's conclusions are valuable in assisting policy makers to decide how best to prevent infertility given our present state of knowledge. Even more important than her substantive results, however, is her demonstration that the process of using available data to determine population-attributable risk (PAR) estimates may be useful in ranking risk factors for infertility. Like record linkage and meta-analysis, this technique is a potentially useful tool for developing a knowledge-based approach to the prevention of infertility.

Conclusion

The studies in this volume contain a great deal of information on the various risk factors for infertility. Taken collectively, however, they also show just how much is still unknown about the prevalence of these risk factors, their relationship to various forms of male and female infertility, and their relative importance. For example, knowledge regarding the cause of mild endometriosis and its possible connection to infertility is limited; and our knowledge of the effects on fertility of the usual levels of exposure to environmental or occupational hazards leaves a great deal to be desired.

This lack of knowledge severely hampers society's ability to effectively prevent infertility. There is sufficient knowledge, however, to come to some conclusions. First, more than enough is known to justify a focus on STDs as the most identifiable and preventable risk to fertility in Canada today. Efforts to prevent STDs and to facilitate early diagnosis and treatment are the single most important step to take in reducing the prevalence of infertility.

Second, we also know enough about the effect of some risk factors on fertility — factors related to particular behaviours — to take action in this area. Any physician, as part of the first approach on seeing patients having trouble conceiving, should ensure that factors such as eating behaviours, excessive exercise, smoking, and use of other drugs have been dealt with before referring the patients for infertility treatment.

Finally, it is clear that further research is needed on various risk factors. Given the diversity of exposures and the various settings in which they occur, this research will entail cooperation by governments, public health workers, environmentalists, employers and workers, and medical and sociological researchers. It is important, too, that researchers take a "synthetic" approach to such research, focussing not only on advances in the study of separate risk factors, but also on the relationships between risk factors and their relative importance. It is only in this way that the prevention of infertility in Canada — the subject of the next volume — can become a reality.



Sexually Transmitted Infections: Their Manifestations and Links to Infertility and Reproductive Illness

Allan R. Ronald and Rosanna W. Peeling



Executive Summary

Sexually transmitted infections are endemic in Canada in 1992; however, many are not reported and their consequences not well documented. Perhaps as many as one in five Canadians become infected with one of these pathogens during their sexually active years. More than 30 pathogens are known to be transmitted sexually, about 10 of which are particularly important because they have significant long-term effects on the reproductive health of women and, to a lesser extent, men. Their impacts on reproductive health include acute and chronic pelvic inflammatory disease (PID); difficulties with conception due to tubal factor infertility; pregnancy wastage due to ectopic pregnancy, spontaneous abortion, and stillbirth; premature delivery; and acute or chronic infections in infants born to infected mothers. In addition, sexually transmitted infections can interfere with sexual health due to psychological or physical factors that adversely alter sensory or emotional experiences.

Tubal infertility probably accounts for 10% to 20% of female infertility in Canada (Collins et al. 1984), most of which is due to the consequences of sexually transmitted infections (Hatcher et al. 1988).

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Over 50% of ectopic pregnancies are considered to be the sequelae of sexually transmitted diseases (STDs). Probably 5% to 15% of spontaneous abortions, stillbirths, premature labour, and neonatal illnesses are due to sexually transmitted pathogens.

Two bacterial pathogens, *Netsserta gonorrhoeae* and *Chlamydia trachomatis*, are responsible for over 50% of the known adverse sequelae within the reproductive tract due to STDs. Genital herpes virus, cytomegalovirus, hepatitis B virus, human immunodeficiency virus, and human papillomavirus are each important viral pathogens, both with regards to their effect on the general health of those they infect and as agents responsible for specific disturbances in reproductive tract function. No effective therapy is available to eradicate any of these pathogens from individuals once infection has occurred; thus, these viral infections are lifelong. As a result, such infections are particularly pernicious as STDs, and their prevention should be one of the highest priorities within public health in Canada today.

Syphilis, due to its global prevalence, remains an important cause of illness during pregnancy and in neonates. In Canada, however, control measures have been quite effective, and it is a relatively uncommon disease.

The control of sexually transmitted infections in Canada is primarily the responsibility of the respective provincial governments. However, the Government of Canada provides direction and leadership. Federal resources are made available to investigate certain disease outbreaks and to support a laboratory reference and disease control centre, which provides expertise to provincial laboratories and individual care providers. The federal government also provides resources to develop guidelines for the management and control of STDs. Research funds are also provided by federal granting agencies.

Interventions undertaken in some other countries, such as Sweden, have dramatically reduced the prevalence and incidence of STDs, particularly *C. trachomatis* and *N. gonorrhoeae*. These programs are now reducing the occurrence of PID and should begin within five years to reduce the incidence of tubal infertility, ectopic pregnancy, and other reproductive health complications of these pathogens.

The success of these programs depends on several currently well-accepted principles of STD control. Public health programs that focus primarily on providing medical services and education to prevent or modify risk behaviour are no longer sufficient. STD control must be closely integrated with social and economic programs that address the issues of poverty, homelessness, and drug addiction. Both the media and the education system need to be involved in a major way in facilitating general public knowledge about sexual health and fulfilment, gender inequality, STDs and their consequences, and the prevention of these infections. Effective management, including diagnostic procedures and effective therapies, must be readily available to all care providers. Health care personnel in all care settings must be knowledgeable and motivated to address enthusiastically risk assessment, counselling about the effects of STDs on reproductive health, and prevention strategies.

Specific groups in society, such as sexually active adolescents, street youths, and other identified "high-risk" groups, need targeted programs designed to assist them in reducing their risk of acquiring and transmitting sexually transmitted pathogens. Canadian youth are experiencing their sexual debut at a younger age, infrequently using condoms for pregnancy or STD prevention, and are thus at risk for acquiring STDs. They are also at markedly increased risk of seguelae damaging to their reproductive health for biologic and demographic reasons. A subset of adolescents change sexual partners frequently and are much more likely to acquire STDs and transmit them to subsequent partners. The risks of STDs and their untoward consequences are markedly increased as well in some socially disadvantaged populations. These populations are marginalized from care programs and have less access to education. As a result, considerable effort must be made to identify these individuals and creatively design programs that meet their priorities and needs.

In some countries, public health authorities have set goals to reduce STDs during the 1990s to ensure that resources are made available for control programs, and that appropriate education and training occur to achieve a dramatic reduction in STDs and their consequences over the next 5 to 10 years. In Canada, most of the components for such a program already exist. Well-coordinated federal and provincial leadership is now required to ensure that programs are effectively led and managed to achieve well-defined, widely shared outcomes. Almost certainly a substantial number of cases, perhaps 75% of PID incidence, should be preventable. Comparable reductions should be reachable for tubal infertility, ectopic pregnancy, and other complications of pregnancy attributable to sexually transmitted pathogens.

Major Points

- STDs and their sequelae are a major public health problem in Canada.
- STDs are preventable and most can be treated.
- The prevention and effective treatment of STDs will avert the sequelae of infertility.
- 15% to 20% of infertility is attributable to STD sequelae.
- The major disease burden is in sexually active 15- to 24-yearolds — in particular, in women who could be suffering from the sequelae of STDs at a time when they desire pregnancy. Targeted programs to screen for and treat STDs, especially in this population, would likely be more cost-effective than to repair the damage using in vitro fertilization procedures.
- Effective data collection should be a priority: lack of good epidemiologic data in Canada means we have inadequate tools to assess the economic and social impact of programs to prevent

- infertility or improve fertility and pregnancy outcome within our health care system.
- Research funding: STD and infertility funding for research currently amounts to less than 0.3% of the total funding for health research in Canada. Increased funding for STDs raises levels of interest and expertise in health care personnel, leading to improved standard of care, and will alleviate unnecessary suffering from the consequences of infertility and suboptimal pregnancy outcome.

Part 1. General Concepts of Sexually Transmitted Diseases

Introduction

Sexually transmitted infections are epidemic in certain segments of Canadian society. These infections can result in ectopic pregnancy, chronic pelvic inflammatory disease (PID), and tubal infertility, major areas in which effective preventive strategies could dramatically reduce, over time, the disease burden implicit to these infections. These pathogens also cause complications of pregnancy that lead to pregnancy wastage, including spontaneous abortions, stillbirth, and premature delivery. In addition, they cause neonatal illness and chronic congenital infections that limit the potential of infants to lead full, healthy lives. It is our view that the major proven potential to reduce infertility is in the control of sexually transmitted infections. We believe that initiatives to recognize the significance of sexually transmitted pathogens and support programs to limit their impact on society are important to Canadians.

This chapter will summarize some historical aspects of sexually transmitted diseases (STDs), identify the pathogens transmitted sexually, and summarize their contribution to reproductive illness. In addition, general principles of epidemiology, including disease transmission, and general principles of control of STDs will be outlined.

Sexually transmitted pathogens are a distinct group of microbial agents that are mostly transmissible only by direct contact. Over 30 pathogens are known to be transmitted sexually (Table 1). About a dozen of these pathogens have the human genital tract as their primary or only reservoir. These organisms generally survive poorly outside the human body. As a result of these unique features, transmission of infection occurs only during sexual intercourse and during birth. Several of the important sexually transmitted pathogens are present in the bloodstream, and blood infused accidentally or for medical reasons can lead to infection.

For centuries, sexually transmitted infections have been recognized to cause genital discharges and genital ulcers. In the seventeenth century, syphilis was seen as a malignant plague, often leading to death. However,

the relationship between sexually transmitted pathogens and reproductive health, including infertility, ectopic pregnancy, and other complications of pregnancy, has been recognized only during the past half century (Weström 1980a). Only during the last decade have well-conducted prospective studies in large populations delineated the proportion of patients having infertility, ectopic pregnancies, and premature birth due to these pathogens.

Table 1. Classification of Sexually Transmitted Disease Agents

1. Bacterial agents:

> Neisseria gonorrhoeae Chlamydia trachomatis Treponema pallidum Haemophilus ducrevi Mycoplasma hominis Ureaplasma urealyticum Calymmatobacterium granulomatis Shigella spp.* Campylobacter spp.* Group B streptococci Bacterial vaginosis-associated organisms Salmonella spp.*

Viral agents:

Human herpes virus 1 and 2 Cytomegalovirus Hepatitis B virus Human papillomaviruses Molluscum contagiosum virus Human immunodeficiency virus 1 and 2 Hepatitis A virus* Human T-cell leukemia virus*

3. Protozoal agents:

Entamoeba histolytica* Giardia lamblia* Trichomonas vaginalis

4. Fungal agents:

Candida albicans (sexual transmission unusual)

Ectoparasites: 5.

Phthirus pubis Sarcoptes scabiei

Transmitted by sexual practices that permit fecal oral transmission.

Infections due to *Treponema pallidum* (syphilis) and *Neisseria gonorrhoeae* dominated venereology until about 1970. Since then, genital herpes virus, human papillomavirus, and *Chlamydia trachomatis* have been recognized as equally important pathogens responsible for acute and chronic reproductive tract illness. During the 1980s the human immunodeficiency virus (HIV) and hepatitis B virus were recognized as sexually transmitted pathogens responsible for a large and growing worldwide disease burden. A summary of these pathogens and their links to infertility is shown in Table 2.

Some pathogens are primarily transmitted sexually among populations in which fecal oral spread occurs because of specific sexual practices. They are identified in Table 1 but will not be discussed further, as they are insignificant with regard to reproductive health. Other pathogens will be discussed less extensively, although they infect the human reproductive tract and cause adverse outcomes of pregnancy. Some sexually transmitted pathogens, such as the agents that cause pubic lice and scabies, will not be discussed because they are not known to affect fertility or pregnancy.

Additional sexually transmitted pathogens will likely be discovered during this decade. Perhaps some will eventually assume equal importance to those currently causing epidemic disease in society. Some studies have suggested that the agents that cause bacterial vaginosis may be sexually transmitted (Spiegel 1991). Other clinical presentations, including some patients with the syndromes of non-gonococcal urethritis, cervicitis, and PID, appear to be sexually transmitted, yet no known pathogen has been identified. A continuing search for new pathogens is necessary and will likely widen our understanding of the extent of disease due to organisms transmitted primarily through sexual intercourse.

Reproductive Health

Reproductive health is a concept that needs to be well understood (Wasserheit 1989) as context for the following discussion. We define reproductive health as encompassing one or all of the following: (1) the ability to enjoy sexual activity without fear of personal illness or transmitting illness to one's partner; (2) the ability to conceive when pregnancy is desired and to prevent conception when pregnancy is unwanted; (3) the experience of a healthy, normal pregnancy and delivery without concern about infection that can injure oneself or the developing fetus; and (4) the delivery of a normal, healthy infant free of infection.

Sexuality is one of the least understood and most complex areas of human behaviour. No one understands very well human sexual nature or motivation, and it remains an intensely personal area. It is also profoundly influenced by societal, cultural, and religious structures within which

Table 2.	Strength	of Associ	ation* [3etween	Sexually	Transmitted Patl	Pathogens,	Infertility,	and Pre	Pregnancy	
Outcom	d										

The state of the s	/o sexually	Cid	infortility	pregnancy	in pregnancy	infection	infertility
ramogen	Hallstillited			66			
BACTERIA							
C. trachomatis	+++	+++	+++	‡ ‡ ‡	‡	‡	+
N. gonorrhoeae	† † †	+++	‡	+++	‡	‡	+
T. pallidum	+++	ı	ı	1	+++	† † †	
H. ducreyi	+++	,	1	1			ı (
Mycoplasma hominis	+	+	+	+(5)	+	+	(2)+
Ureaplasma urealyticum	+++	+	+	+(3)	+	+	+(3)
Group B streptococci	+	٠	1	1	+	‡ ‡	ı
Enteric bacteria	1	+	ı		r	•	•
Bacterial vaginosis**	+	•	ı	ŧ	+	+	1
Anaerobic bacteria	-(¿)	+	+	+	ı	\$	•
VIRUSES							
Cytomegalovirus	+		ı		+	‡	1
Hepatitis viruses	‡	1	1	•	1	‡	•
Herpes simplex 2	‡	ı	ı	1	+	‡	1
^I	‡ ‡	ı	ı	ı	‡	+++	,
Human papillomaviruses	‡	ŧ	1	1	ŧ	+	
PROTOZOA							
Trichomonas vaginalis	+	٠	ı	-	+	+	1

This is a syndrome, diagnosed clinically, which is associated with the isolation of several bacteria, none of which has been proven to be sexually transmitted.

individuals and society function. Sexual health is a recent concept that only now is being developed within the health care and educational systems as a concept that needs to be effectively communicated to all Canadians. This needs to occur within structures that ensure that many social values are enhanced and affirmed. STDs tend to become epidemic during rapid societal changes in sexual "norms" or other changes that increase sexual interaction (Brandt 1985; Aral and Holmes 1990).

STDs and Reproductive Health

STDs may affect reproductive health in at least eight ways:

- The fear of STDs and their occurrence can result in a loss of interest in sexual activity and physical pain or dyspareunia with intercourse. The latter is a common complication in women and probably not infrequent in men.
- STDs in the lower genital tract can lead to urethral, penile, vulval, vaginal, or cervical inflammation. The primary complications of infections at these sites, depending on the pathogen, are urethral discharge, genital ulceration, vaginal discharge, and pelvic discomfort or pain. Both the cervix and the vagina are relatively poorly supplied with pain fibres; thus, pain is less intense in either of these structures despite moderately severe signs of inflammation. However, the primary concern of infection in the lower genital tract is its propensity to infect the upper genital tract.
- STDs produce genital inflammation within the upper genital tract, including endometritis, salpingitis, oophoritis, and infection of contiguous organs within the pelvis. This is referred to generally as PID. In men, urethritis can also involve the epididymis and other genital organs.
- STDs as either clinically apparent or asymptomatic PID may lead to tubal malfunction and, in advanced cases, to tubal obstruction. This pathology, in turn, may result in ectopic pregnancy or infertility due to "tubal factor."
- STDs may infect the placenta, the membranes lining the uterus, or the fetus itself to produce spontaneous abortion, stillbirth, or premature labour.
- STDs may infect the live-born infant so that illness is present either during the neonatal period or on into infancy and childhood.
- Some STDs can enter via the genital tract without any overt evidence of genital infection. However, illness at distant sites occurs and can be either acute or chronic. Syphilis, HIV,

- hepatitis B virus, and cytomegalovirus (CMV) are examples of this phenomenon.
- STDs are occasionally responsible for male infertility by causing reduced spermatogenesis, or a failure of transmission of the spermatozoa from the testes through to the urethra.

Sexual Behaviour and STDs

Sexual behaviour involves many components in addition to number of sexual partners. The age of sexual debut is an important variable. Numerous studies have suggested that acquisition of STDs and some complications of STDs including cervical dysplasia and PID are more common during the adolescent years. Also, risk of exposure to a STD depends not only on the number of sexual partners but also on the choice of partners. The choice of sexual partners is probably as important as the number with regard to risk of acquiring STDs, but how they are chosen is still not well understood.

Whereas some people are at risk for STDs because of their own sexual behaviour, others are at risk because of their partners' behaviour. The likelihood of the former becoming infected is high because of contact with a partner at high risk of getting infection. Conversely, their risk of transmitting the infection is low. Women are more frequently in the category of "STD receivers."

Women's health has not received the priority it should in Canada. Too often women do not have control over their choices of sexual partners or the safety of sexual relations. For economic, cultural, or other reasons they may be forced to accept the risk of getting a STD, which places them or their future pregnancies at substantial risk. Strategies to improve the overall status of women in society and to increase their economic and legal status are probably as important as specific programs directed toward the reproductive health of women and the control of STDs. However, this document will only focus specifically on ways of improving reproductive health and STDs.

Although the present situation is serious, there are societal reasons for considerable hope that reproductive tract infections, specifically STDs in women, can be more effectively controlled. They include:

- the growing realization by many that reproductive tract infections are not only a serious health problem to the individual but have serious societal and economic consequences;
- the changing view of women in society, including an increasing number of initiatives to improve their legal, economic, and social welfare:
- the substantial allocation of funds for the control of HIV, which should have a favourable impact on other STDs (e.g., gonococcal

- infection and syphilis have decreased dramatically in many industrialized countries during the 1980s);
- the realization that existing programs in maternal and child health, family planning, and primary health care can be merged to achieve a synergy that will improve reproductive health;
- an increasing realization that allocation of resources for health research may result in insights allowing the implementation of effective programs; and
- the recognition that health care systems must have input from community structures and that women must be given increasing authority to determine their own priorities in health care, thus allowing more effective and appropriate strategies to be implemented.

Epidemiology of Sexually Transmitted Pathogens

Historically, sexually transmitted pathogens have been associated with population disruptions such as those due to war, famine, or other causes of large population migration. Although no such major disruptions occurred in the 1960s and 1970s, changes in contraception practices and sexual behaviour became widespread throughout the industrialized world, including Canada. As a result, there was a dramatic increase in infections due to *N. gonorrhoeae* and probably *C. trachomatis*, human papillomavirus, and genital herpes (see Part 2, Figures 3a, 3b, and 5). The legacy of this epidemic of sexually transmitted infections is the rapid increase in the incidence of long-term sequelae, including ectopic pregnancy, tubal infertility, and cervical dysplasia.

Figure 1 depicts the reported communicable diseases in Canada in 1990. Over 50% of reported communicable infections in Canada are sexually transmitted.

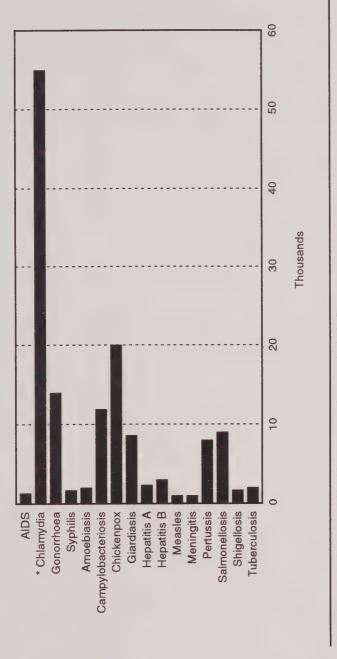
The transmission dynamics of sexually transmitted pathogens have been carefully articulated by May and Anderson (1988) and can be simply understood on the basis of an equation:

$$R_0 = \beta cD$$

 $R_{\scriptscriptstyle 0}$ is a measure of the reproductive rate of new infections. If $R_{\scriptscriptstyle 0}$ can be reduced to less than one for a prolonged period, the chain of transmission is ultimately ended and the disease will "die out" over time. As a result, it is appropriate to understand each of the three variables that account for the size of $R_{\scriptscriptstyle 0}$, and to attempt to understand how they can be modified to achieve infection control and ultimately disease eradication by reducing $R_{\scriptscriptstyle 0}$ to less than one.

 β measures transmissibility of a pathogen. This depends on sexual practices, frequency of exposure to infected individuals, and susceptibility





(Only diseases where annual incidence exceeds 1 000 included) * Excludes British Columbia and the Northwest Territories.

Source: Laboratory Centre for Disease Control, Health and Welfare Canada.

of the individual at risk of acquiring the infection. Many of these factors are not well understood. However, the use of barrier contraceptives, such as condoms, reduces the risk of transmissibility and thereby reduces β . A vaccine that reduces susceptibility would also reduce β ; however, hepatitis B virus is the only sexually transmitted pathogen for which a vaccine is currently available. Some STDs are very transmissible during unprotected genital heterosexual intercourse (e.g., a man with urethral *N. gonorrhoeae* infection will likely infect one-half of the women with whom he has unprotected sex).

The parameter c measures the number of new sexual partners. Sexual behavioural surveys in the United States have suggested that 80% of sexually active individuals have had at most one partner during the previous 12 months (Biggar et al. 1989). Analyses of the results of a cross-Canada survey of community college and university students by MacDonald et al. (1990) showed that 74% of men and 69% of women (mean age = 19.7 years) are sexually active. Only 25% of men and 16% of women always use a condom despite "an adequate" knowledge of HIV infection and other STDs. Of the men (21%) and women (7%) with 10 or more partners, 1 in

9 men and 1 in 4 women had a history of STDs.

People who have few or no partner changes have little impact on the epidemiology of STDs. Ultimately, the small proportion of people who have had numerous partners become the "reservoir" and the "vehicle" that maintain sexually transmitted pathogens in society. In Canada, this group probably represents less than 3% of sexually active individuals (men likely exceed women in this group by 2:1). These groups are often referred to as core groups or high-frequency transmitter groups, but there is no universally accepted definition. Five or more partners per year may put one in this category if "safer sex" is not routinely practised. Many of these individuals are infected with one or more sexually transmitted pathogens, and the presence of these pathogens further defines subsets in the core group. In the industrialized world, such groups are often young, poor, and non-white and have limited access to health care (Aral and Holmes 1990). People who sell sex and intravenous drug users are frequently members of this vulnerable group.

As an example, in the province of Manitoba with a population at risk of about one half million sexually active adults, it has been estimated that the core group with gonococcal infection may be as low as 1 250 (Brunham and Plummer 1990). This group would be defined as individuals infected with this particular pathogen who because of their sexual behaviour are likely to pass this pathogen on to other individuals. Core groups have also been shown to be important in the transmission of syphilis and HIV; in Manitoba each of these core groups probably comprises fewer than 100 individuals. On the other hand, the core groups at high risk of transmitting *C. trachomatis*, herpes simplex, and human papillomavirus infection are probably 10 or more times greater than that for gonococcal infection. The numbers for these core groups are estimates only, and more epidemiologic

research is needed to determine their dimensions. However, the core group concept is important for STD control. To be successful, STD programs must focus on core groups with innovative educational messages, control strategies, and care programs that offer job opportunities, low-cost housing for the homeless, and treatment for drug addiction. If the prevalence of infection can be reduced in these groups, some, perhaps many, STDs will gradually disappear.

D is the duration of infection. Acutely ill and symptomatic patients often will not be sexually active and, therefore, will be poor disseminators of infection to new partners. However, most sexually transmitted pathogens cause prolonged periods of asymptomatic carriage within both the male and female genital tracts of people who are otherwise well and who continue to be sexually active. Usually, asymptomatic individuals have no reason to seek medical attention or be examined for infection unless they are reported by their partners to be a source of infection. Programs designed to treat asymptomatic contacts or screen and treat symptomatic infected individuals can reduce D. HIV is particularly troublesome because of its long latency or incubation period (or very prolonged D). Many HIV-infected persons may live for 15 years or more without a clinical diagnosis of infection, and are presumably infectious for any sexual partner throughout these years. This may apply to all individuals with viral STDs.

General Control Strategies for Sexually Transmitted Pathogens

Once the above aspects of epidemiology of sexually transmitted infections are understood, control strategies become apparent. They are usually considered as primary, secondary, and tertiary intervention targets.

Primary intervention is designed to prevent the acquisition of STDs and is directed toward all three important variables, i.e., reducing the rate of new partner acquisition (c), reducing the rate of transmission (β), and limiting the duration of infection (D).

Primary Prevention Strategies

Reducing the rate of new sexual partner acquisition requires broadly directed and effective messages to all sexually active people. This education would need to begin in primary school before students are sexually active. The message must continue to reach people at the highest rates of sexual partner change (i.e., adolescents and young adults not in stable relationships, especially those whose lifestyle and sexual behaviour fit into the previously defined core group). As these people are usually difficult to reach, outreach programs and innovative community-based initiatives are required. Also, factors that provide sexual satisfaction within monogamous relationships need to be studied to facilitate individuals entering ongoing, supportive, long-term relationships. Such relationships should markedly reduce the risk of STDs for couples and for society.

Strategies to influence transmissibility are increasingly available and reasonably effective. Studies to evaluate and increase the acceptability and effectiveness of condoms are required. The risks of specific sexual practices need to be determined and education provided to ensure that people at risk take precautions to avoid infection. Programs of public education on non-volitional sexual contact such as in child sexual abuse or rape and the provision of preventive and treatment services as recommended by the Bagley Report (Canada, Committee on Sexual Offences 1984) are also important. Ultimately, vaccines may be developed that will substantially decrease susceptibility and sharply alter the transmissibility of STDs. Vaccines have the potential to be effective if protective host responses can be identified through basic research.

Secondary Prevention Strategies

Secondary prevention strategies, as well as a public health strategy to reduce the transmission of STDs, are directed toward individuals who have acquired a STD. Programs to reduce the duration (D) of infections are currently a high priority within the Canadian health care system. Screening programs to identify people who have asymptomatic infections, partner referral to identify and treat contacts, and educational programs to encourage health-seeking behaviour in those at risk of STDs are all important strategies to reduce the duration of infectiousness and thereby alter transmission patterns.

A second goal is to identify and treat infections early, particularly in women, before upper genital tract invasion and damage have occurred. This is especially true of STDs for which curative therapy exists. This requires appropriate health care facilities, education programs to encourage use of these programs, and user-friendly diagnostic techniques and treatment regimens. In particular, contact during routine ante-natal care, the provision of family-planning services, and care for other unrelated illnesses offer opportunities to assess sexual risk and, if indicated, diagnose treatable infections such as gonococci, chlamydia, and syphilis. These programs are currently being implemented in the primary care system throughout Canada and may be very effective in reducing sexually transmitted infections.

Tertiary Prevention Strategies

Tertiary prevention is the prevention of STD progression to damaging "permanent" sequelae and remedial treatment when damage has occurred. Present *in vitro* fertilization (IVF) procedures can cost more than \$60 000 per live birth and have limited efficacy (Cooper 1986; Vutyavanich and Collins 1991). Research directed at identifying and delineating the mechanism of functional and structural injury to the genital tract as a result of STDs should be a priority. Prospective studies and basic research into understanding the causes and risk factors for ascending genital tract disease due to sexually transmitted pathogens are needed for effective intervention.

Part 2. Sexually Transmitted Pathogens

Introduction

This section details current knowledge of the sexually transmitted pathogens identified in Part 1 (Table 1) as major contributors to infertility and suboptimal pregnancy outcome. Fundamental knowledge of the pathogens is important to understand the mechanisms by which they cause disease and how acquisition and transmission of infection can be prevented.

Each pathogen is discussed under the following headings:

Introduction: A brief description of the micro-organism.

Epidemiology: Prevalence of infection in Canada where available, mode of transmission, and risk factors for acquisition of infection.

Clinical Manifestations and Links to Infertility: These include tubal infertility, male infertility, suboptimal pregnancy outcome, and congenital and neonatal infections. Links of STDs to infertility are often tenuous for the following reasons:

- 1. sequelae usually occur long after the primary infection;
- 2. sampling sites, e.g., fallopian tubes, are inaccessible without invasive procedure;
- 3. host-mediated (immune) damage is complex, is poorly understood, and may be not pathogen specific, i.e., the damage can be caused by other factors; and
- 4. treatment efficacy is difficult to evaluate due to a lack of non-invasive diagnostic methods.

Thus, in this review the links have been established through studies of the following nature:

- 1. the direct demonstration of a pathogen in affected tissue, implying causal relationship;
- 2. epidemiologic surrogate markers; and
- 3. by inference through successful specific treatment.

Diagnosis: Clinical and laboratory diagnosis. Some general comments on laboratory tests used for the diagnosis of STDs (all estimates of laboratory tests are the authors'):

Culture — usually the method of choice or "gold standard" as it
is highly specific and the isolate can then be used for antimicrobial susceptibility testing and epidemiologic or legal
purposes.

- Microscopy direct visualization of the pathogen with or without staining.
- Antigen detection the pathogen is captured on a solid support
 primed with an antibody specific for a component on the surface
 of the pathogen. A detector antibody conjugated to a fluorescent
 dye or an enzyme that can react with a coloured substrate is then
 added to detect a positive reaction.
- Serology detection of antibodies to a pathogen in the blood of an infected person as an indicator of exposure to that pathogen.
- Gene probes detection of the genetic material of a pathogen present in a specimen. The sensitivity of this method can be increased by amplification of the nucleic acid using the polymerase chain reaction.

The cost and the range of sensitivity and specificity of each method are given where possible. Whenever batching is possible, the cost per specimen decreases as the number of specimens processed by a given laboratory increases. The performance of a test is measured by its sensitivity and specificity. The predictive value of a test is related to the prevalence of infection in the population.

Interventions: Treatment; vaccines; and prevention and control strategies. Research Priorities: Identification of current research trends and areas in need of solutions.

1. Chlamydia trachomatis

Introduction

Chlamydia trachomatis is a bacterium that can reproduce only inside mammalian host cells. It is an "energy parasite" in that it is largely dependent on the host cell for energy to fuel its metabolism and reproduction. Chlamydiae are predominantly human pathogens, except for *C. psittaci*, which causes illnesses such as parrot fever and sheep abortion.

Epidemiology

C. trachomatis is now recognized as one of the most prevalent sexually transmitted pathogens in Canada. Statistics from 1980-89 compiled through a voluntary reporting system from many Canadian laboratories are shown in Table 3. The main limitations to this method of data collection are (1) different laboratories report to the system every year; (2) the number of laboratories reporting varies from year to year; and (3) the total number of specimens submitted for testing is not recorded. Hence, a percent positive rate cannot be calculated to estimate trends. The figures in Table 3 underestimate the number of chlamydial infections in Canada as they include only those individuals on whom positive laboratory diagnoses were made. In addition, clinical syndromes due to C. trachomatis, such as

urethritis and cervicitis, are not reportable in most areas of Canada. The increasing availability of user-friendly non-culture detection tests from 1984 onward is reflected in the dramatic increase in positive findings of chlamydial infections in subsequent years.

Chlamydial infections became nationally notifiable in 1990. Although they have been reportable in some provinces since as early as 1983, they are still not legally reportable in Newfoundland and New Brunswick. Figure 2 shows the reported rates of chlamydial infections in Canada for 1989-1990, analyzed by age and sex. Over 70% of the reports involved 15to 24-year-olds, of whom 80% were female in the 15- to 19-year age group.

The prevalence of genital chlamydial infections in Canada in specific settings has been compiled from a selection of studies published over the last 10 years (Table 4): they varied from over 25% at STD clinics, to 14% in family-planning clinics, to 5% to 7% at student health clinics. The ratio of chlamydial to gonococcal infections in different study populations varied from 0.8:1 to 13:1.

Table 3. Laboratory Reports of Chlamydial Infections in Canada, 1980-89

Year	No. centres contributing*	Frequency of positive findings**		
1980	7	1 881		
1981	9	1 938		
1982	10	1 680		
1983	11	1 435		
1984	16	4 371		
1985	19	8 108		
1986	18	9 661		
1987	17	9 776		
1988	18	9 179		
1989	29	13 369		

^{*} Centres include provincial laboratories in most provinces, some regional health laboratories, and university and general hospital laboratories.

Source: Compiled by authors based on data collected by the Bureau of Microbiology, Laboratory Centre for Disease Control, Health and Welfare Canada.

^{**} The number of specimens submitted is not reported. Diagnoses by culture, antigen detection tests, and serology are all included.

Illustrative Case — The Missed C. trachomatis Infection

Agnes is an 18-year-old Grade 12 student who presents her primary care physician with a three-day history of fever, lower abdominal pain, and vomiting. Her last menstrual period ended three days earlier.

She has become sexually active only during the past year and has had only two sexual partners. Her most recent relationship began two weeks earlier. To her knowledge neither of her partners has had any symptomatic illness. She uses no contraceptive and her sexual partners have not used condoms. She avoids pregnancy by not dating during her "fertile period." All episodes of coitus have been genital.

Pelvic examination disclosed an acute purulent cervicitis with severe pain on cervical motion. Also, the left adnexal area was extremely painful and a diffuse swelling was noted. Her temperature was 39°C. Cultures were obtained from the

cervix.

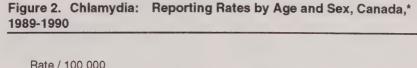
She was immediately started on cefixime, an oral cephalosporin, effective against gonococci. Within 48 hours she was markedly improved. The laboratory called to notify the physician that the cervical cultures were positive for N. gonorrhoeae.

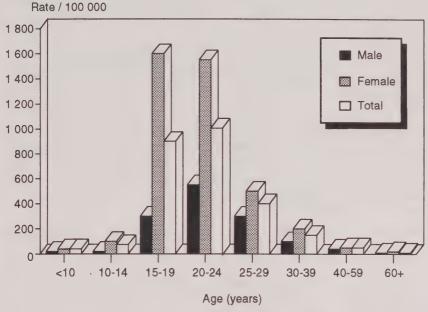
The next day her physician prescribed by telephone the same medication for her boyfriend without an interview or examination.

Ten days later a report arrived on the physician's desk noting *C. trachomatis* was also cultured. A single attempt to notify the patient failed to find her at home, and no subsequent treatment occurred.

Learning Points

- Many caregivers fail to consider C. trachomatis as an inciting or concomitant infecting agent in women with PID.
- Failure to treat both individuals for C. trachomatis may lead to subsequent spread of this pathogen to other sexual partners in the future.
- Failure to interview and obtain additional history from the patient's boyfriend prevented other contacts being identified from the chain of transmission, who may be at risk from either N. gonorrhoeae or C. trachomatis.
- This patient has a substantial risk of presenting herself several years later with either tubal infertility or ectopic pregnancy. At that time, any direct relationship to her current illness or to the infection with C. trachomatis may not be noted.
- Clinically evident PID resolves in most women regardless of whether the antibiotics selected are effective. Frequently, patients and their caregivers assume that improvement has resulted because of the correct choice of antibiotic agent; this is often an incorrect assumption.
- The physician did not request help from resources provided by the public health service. When Agnes was contacted by the public health service, they were informed that the physician had done the contact tracing and treated all partners.





Excludes British Columbia and the Northwest Territories. Source: P.R. Gully and D.K. Rwetsiba, "Chlamydial Infection in Canada." Canada Diseases Weekly Report 17 (21 December 1991), 287.

These Canadian studies, similar to studies elsewhere, showed that over 50% of infected women are asymptomatic. Until a non-invasive screening test is developed for men, the corresponding figure for men will not be known. The high rate of asymptomatic carriage and the inconsistency of reporting imply that the true disease incidence may be two to three times greater than that reported; thus, over 50% of chlamydial infections in Canada will not be detected unless targeted screening is implemented. Asymptomatic infections may progress to silent PID and subsequent infertility or ectopic pregnancy.

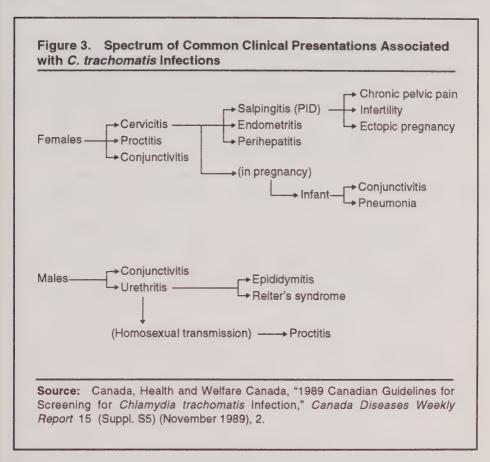
Risk factors associated with chlamydial infection include young age, two or more sex partners in the previous 12 months, or a new partner in the last 60 days. Unlike STDs such as gonorrhoea and syphilis, chlamydial infections are not concentrated in any particular socioeconomic class or ethnic group (Thompson and Washington 1983; Aral and Holmes 1991).

		Detection	Prevalence (%)		
Authors (study period, locale)	Study population	method	Ct*	Gc**	Ratio
Bowie and Jones (1981) (1978-1980, Vancouver, BC)	830¥ STD clinic	culture	22	10	2.2:1
Sorbie and O'Shaughnessy (1982) (1979-1980, Ottawa, ON)	Family practice, 1009 symptomatic, 309 asymptomatic	culture culture	30 7	0	-
Bowie et al. (1981) (1980, Vancouver, BC)	4529 STD clinic, 1239 Student health, 67-70 symptomatic	culture culture	25 7	8	3:1
Embil and Pereira (1985) (1980-81, Halifax, NS)	355º Family planning, 136º Prenatal clinic, asymptomatic	culture culture	7.2 3	-	
Pereira et al. (1990) (1983-85, Halifax, NS)	247º STD clinic, asymptomatic	culture	27.1	37.8	0.8:1
Noble et al. (1988) (1984-86, Vancouver, BC)	1 220º University health, symptomatic, 2 539º University health, asymptomatic		7.1-8.2 5-6	0	
Levallois et al. (1987) (1985-86, Montreal, PQ)	920¥ Abortion clinic, asymptomatic	EIA	11.4	0.9	12.7:1
Hughes et al. (1989) (1986, Ottawa, ON)	39) (1986, asymptomatic		14.8	1.8	8:1
Binns et al. (1988) (Winnipeg, MB)	520¥ Pregnancy counselling, asymptomatic	culture	10.8	-	
Vincelette et al. (1991) (1986-87, Montreal, PQ)	2 856 Patients at risk of STD or presenting for abortion	EIA	15-24 yrs 21.9& 15.6\$	15-24 yr 7.4 ♂ 1.6♀	s 3:1 10:1

^{*} Ct — Chlamydia trachomatis infections.
** Gc — Neisseria gonorrhoeae infections.

Clinical Manifestations

The incubation period for chlamydial infection is estimated to be 7 to 21 days. As infection is often asymptomatic, accurate calculation of the incubation period, particularly in women, is uncertain. The spectrum of clinical manifestations of infections caused by *C. trachomatis* is shown in Figure 3.



Links to Infertility

Cates and Wasserheit (1991) reviewed the reproductive sequelae for genital chlamydial infections based on studies from 14 countries in the last 20 years and found a significant association between the development of PID and ectopic pregnancy and the presence of chlamydia antibodies in serum. Infection elicits an inflammatory response in the pelvic area. Healing results in scar tissue, which builds up from repeated cycles of inflammation and healing, resulting in occlusion of the fallopian tubes: hence, tubal infertility or ectopic pregnancy. Most of the tissue damage associated with chlamydial infections is likely mediated by the immune

responses of the host (Morrison 1990). Thus, immune response to chlamydial infections may be a double-edged sword in that while antibody response to the chlamydial major outer membrane protein neutralizes infectivity *in vitro* and may be protective, response to a heat shock protein on the chlamydial outer membrane has been shown to be correlated with the development of PID and ectopic pregnancy (Wagar et al. 1990; Brunham et al. 1992).

Pelvic Inflammatory Disease and Tubal Infertility

Studies in the last two decades have implicated *C. trachomatis* in 30% to 60% of PIDs due to exogenous sexually transmitted pathogens. Studies by Svensson et al. (1980) and Patton and Kuo (1989) showed that PID is a consequence of chlamydial cervical infection, and Safrin et al. (1990) found that 31% of 74 women surveyed 37 months after documented PID were involuntarily infertile.

Concomitant chlamydial infections are found in 30% to 50% of women with gonococcal infection. Bowie and Jones (1981) showed that women with concomitant infections more frequently develop PID than women with either infection alone. Batteiger et al. (1989) found that same-strain recurrences are more frequent in patients with concomitant infections, suggesting that the gonococcus may reactivate latent chlamydial infection.

Compared to gonococcal PID, the clinical presentation of chlamydial PID is more insidious, less acute, and often clinically unapparent. Results of studies in Canada and elsewhere have shown that over 60% of women with chlamydial PID are asymptomatic; hence, their disease may progress undetected to silent PID, ectopic pregnancy, or tubal infertility (Gump et al. 1983; Sellors et al. 1988).

C. trachomatis is a major cause of tubal infertility. The evidence is based largely on strong correlations of tubal infertility with high levels of chlamydial antibody, which is indicative of past infection (Moore et al. 1982; Jones et al. 1982; Brunham et al. 1985; Sellors et al. 1988). In Hamilton, Ontario, 69% of 265 women investigated for tubal infertility did not recall a history of PID. Antibodies to C. trachomatis were detected in over 70% of these women compared to about 35% of women with non-tubal factor infertility. Infectious chlamydiae were cultured from 15% to 35% of tubal biopsies or swab sampling of the upper genital tract from 52 and 111 women, respectively (Shepard and Jones 1989; Henry-Suchet et al. 1987). The failure to detect the organism in tubal tissues may mean that viable organisms are not necessary to sustain the inflammatory process or that the detection techniques are not sensitive enough for low-grade infections. If the former is true, it would suggest that damage, once initiated, is irreversible regardless of whether the infection is spontaneously cleared or eradicated by therapy. C. trachomatis has been shown to persist for 15 months if untreated, and for 4 years in an infertile couple (McCormack et al. 1979; Ruijs et al. 1990).

Ectopic Pregnancy

C. trachomatis is a common infectious cause of ectopic pregnancy as a result of chronic PID. Results of a study in Winnipeg, Manitoba, showed that one-third of ectopic pregnancies may be due to chlamydial infections (Brunham et al. 1986). In 16 studies, 19% to 95% of cases of ectopic pregnancy had histologic evidence of prior PID. Since a large proportion of PID is attributable to C. trachomatis, it is likely also a common cause of ectopic pregnancy. In longitudinal cohort studies, Weström et al. (1981) demonstrated that women who had acute PID were at 7 to 10 times greater risk for ectopic pregnancy. Women without an underlying risk factor for ectopic pregnancy, such as intrauterine device (IUD) use or tubal ligation, are found to have C. trachomatis antibodies significantly more often than control groups. Active tubal chlamydial infection cannot be demonstrated with isolation in culture, but more sensitive detection techniques using amplification of chlamydial genes in the damaged cells may provide the definitive proof of chlamydial etiology for ectopic pregnancy.

Male Infertility

C. trachomatis is a cause of epididymitis in men; however, the links to male infertility have not been proven.

Adverse Pregnancy Outcome

The issue of whether chlamydiae cause any suboptimal pregnancy outcome for the mother and child is controversial. Post-partum endometritis may be associated with chlamydial infection during the third trimester or at delivery. The results of several studies have suggested that chlamydial infections during pregnancy were associated with second-trimester abortion, stillbirth, neonatal death, prematurity, or low birthweight (Investigators of the Johns Hopkins Study 1989; Martin et al. 1982; Harrison et al. 1983). Such findings have not been confirmed in other studies. Cohen et al. (1990) reported improved pregnancy outcomes of premature delivery, premature membrane rupture, premature contraction, and small-for-gestation age in 244 pregnant women following successful erythromycin treatment of chlamydial infection.

Estimates of the probability of transmission of chlamydia from an infected mother to the newborn range from 5% to 35%. In Canada, 40% of the ocular infections and 73% of the respiratory infections due to *C. trachomatis* are in infants under six months of age, which suggests a perinatal route of transmission (Canada, Health and Welfare Canada 1989a).

Animal Models of Chlamydial Infections

Current knowledge of the progression from acute lower genital tract chlamydial infection to inflammation in the pelvic area and eventual occlusion of the fallopian tubes in humans is limited due to difficulties in follow-up after primary infection. This is complicated by the large number of asymptomatic cervical infections and silent PID due to *C. trachomatis*.

Prospective studies in experimental animals allow for detailed histological and immunological examination at each stage of the infection. Patton et al. (1987) and Patton and Kuo (1989) showed in female pig-tailed macaques that tubal edema can occur after the first cervical inoculation. Repeated chlamydial infection produced extensive tubal scarring, chronic PID, and obstruction distal to the site of inoculation. Again, infectious organisms are not isolated from the site, but the presence of chlamydial proteins and deoxyribonucleic acid (DNA) can be demonstrated.

Does immunity to chlamydia lead to some of the adverse outcomes of this infection? Tuffrey et al. (1985) and Tuffrey and Taylor-Robinson (1990) demonstrated in mice that PID developed despite the presence of pre-existing antibodies to chlamydia. Although a second infection was cleared more rapidly that the primary infection, which is evidence of protective immunity, the mice were still susceptible to re-infection, and to the development of reproductive sequelae.

Diagnosis

Clinical Diagnosis

Clinical diagnosis of uncomplicated genital infections of *C. trachomatis* is based on symptoms of urethral or cervical discharge, and easily induced endocervical bleeding. The presence of 5 to 10 white blood cells per high-power microscope field from a urethral or endocervical smear is suggestive of a chlamydial infection. The infection may mimic diseases of other etiologies, such as urinary tract infections or cystitis. Complications may occur without fever or increased white cell count. Thus, misdiagnosis or failure to seek treatment may be common.

Laboratory Diagnosis

The performance characteristics, advantages, and disadvantages of different methods for the laboratory diagnosis of chlamydial infections are summarized in Table 5. Culture of *C. trachomatis* requires a great deal of technical expertise. Thus, standards may vary from laboratory to laboratory. Sensitivity and specificity for the newer generations of direct fluorescent antibody (DFA) and enzyme immunoassay (EIA) technologies approach 75% and 95%, and 90% and 99%, respectively. Urine is now tested in EIA as an alternative to urethral swabs. Although urine EIA is currently less sensitive (60% to 80%) than EIA on urethral swabs, it offers a non-invasive method to screen or diagnose chlamydial infection in men. The cost of culture is \$15 to \$20, compared to \$5 to \$10 for non-culture tests such as DFA and EIA.

Interventions

Treatment

Chlamydial infections can be treated successfully with a seven-day course of tetracycline or erythromycin. Non-compliance may be a problem as symptoms often resolve within a few days. Thus, because "test of cure"

Table 5. Summary of the Attributes of Laboratory Tests for the Diagnosis of *Chlamydia trachomatis* Infection

Feature	Tissue culture	DFA*	EIA**
Specimen site usage	all	cervix urethra conjunctiva	cervix urethra
Sensitivity	75-80%	65%	65%
Specificity	100%	70-95%	85-97%
Specimen transport temperature	refrigerate (do not freeze)	ambient	ambient
Maximum time to laboratory	24 hrs	7 days	48 hrs
Collection kits available from	tissue culture laboratory	testing laboratories	testing laboratories
Suitable for legal purposes?	yes (due to specificity)	no [†]	no
Report available in	minimum 48 hrs	24 hrs	24 hrs
Verification of specimen adequacy	no	yes	no
Stat testing possible?	no	yes	no
Costs - Labour - Per test	high/increasing high	lower lower	lower lower
Test interpretation	subjective	subjective	objective

^{*} DFA — Direct Fluorescent Antibody.

Source: Canada, Health and Welfare Canada, "1989 Canadian Guidelines for Screening for *Chlamydia trachomatis* Infection," *Canada Diseases Weekly Report* 15 (Suppl. S5) (November 1989), 4.

cultures are not usually done, inadequately treated infections may persist. Treatment failures or persistence of primary infections are also difficult to distinguish from re-infection. In addition, the recently reported emergence of strains that are resistant to tetracycline, erythromycin, and clindamycin is a concern (Jones et al. 1990).

^{**} EIA — Enzyme Immunoassay.

[†] May be suitable for clinical purposes, but may not satisfy legal requirements.

Without diagnostic services, epidemiologic treatment can be made on the basis of clinical signs, demography, and behavioural characteristics.

Swenson et al. (1986) used mice to show that treatment with tetracycline prevented tubal pathology only if initiated within two days of inoculation. Treatment after one week of infection prevented permanent tubal damage in some mice, while the fertility outcome for mice treated two weeks after inoculation was not significantly different from that in the untreated controls, where 9 of 10 infected mice became infertile. These experiments demonstrate the need for primary prevention, screening, and specific diagnosis early in the course of infection so that appropriate treatment can be given to prevent adverse reproductive outcomes.

Vaccine

A vaccine has been sought for the eradication of trachoma. Early vaccine trial using whole chlamydiae led to worse disease on re-infection. Research for a component or genetically engineered vaccine that excludes proteins that evoke inflammation and damage, but is capable of eliciting protective immune responses at mucosal surfaces and in blood, is ongoing.

Prevention

Chlamydial infection is a major public health burden because it causes (1) a wide spectrum of diseases; (2) a high proportion of silent infections; and (3) serious long-term sequelae, not the least of which is infertility.

Sustainable primary intervention for chlamydial infection should be through the continual promotion of risk-lowering behaviour, especially in sexually active adolescents, to prevent the acquisition of infection.

For a STD such as chlamydial infection, for which there is effective antibiotic therapy, the most cost-effective intervention is early diagnosis and provision of appropriate therapy. The high proportion of silent infections and the serious personal and economic costs of the long-term sequelae due to undetected or untreated infections are compelling reasons to target screening programs for people at high risk of acquiring and transmitting infection. Contact tracing and treatment of sexual partners is also an important secondary intervention strategy. In Gävk, Sweden, the rate of chlamydial infection in pregnant women less than 21 years of age dropped from 18.8% in 1984-85 to 2.4% in 1988 as a result of the work of Youth Counselling Services in education, contact tracing, and treatment of sexual partners (Thejls et al. 1991).

In terms of tertiary prevention, adequate treatment for and research into the prevention of development of sequelae in people with acute infection are required.

Research Priorities

Little is known about how the organisms ascend the upper genital tract and whether an active infection is necessary for the inflammmatory

process associated with long-term sequelae. Current research priorities are:

- identification of mechanisms of chlamydial attachment and uptake into host cells;
- diagnosis of asymptomatic or silent infections and particularly non-invasive methods to screen for silent infections in men;
- determination of the role of the host immune response in disease sequelae;
- delineation of components of chlamydiae that evoke protective immune responses to clear and limit the spread of infection and components that cause damaging sequelae; and
- determination of the role of the chlamydial heat shock proteins and host response in immunopathology following chlamydial infection.

2. Neisseria gonorrhoeae

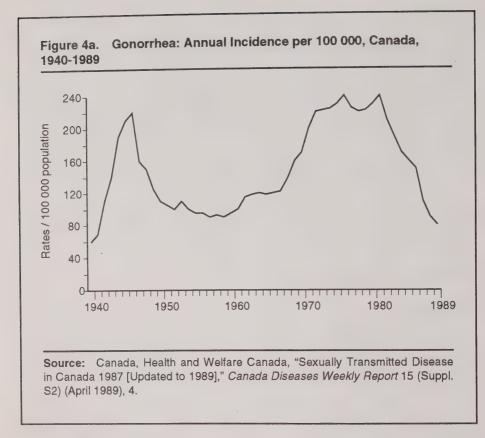
Introduction

Neisseria gonorrhoeae or the gonococcus is a coccoid-shaped bacterium that belongs to the genus Neisseria. Most other species are non-pathogenic for humans with the exception of Neisseria meningitidis, one of the etiologic agents of bacterial meningitis. N. gonorrhoeae is only a human pathogen, and survives for only a short time outside the human body. There is no evidence for transmission other than by intimate physical contact with the mucosal surfaces of an infected person. Babies born to infected mothers usually acquire eye infections, which, if untreated, may lead to blindness.

Epidemiology

Gonococcal infections have been reportable in Canada since 1940. The incidence of gonorrhoea in Canada has declined since the 1980s, probably as a result of the fear of acquired immunodeficiency syndrome (AIDS) and increased awareness of STDs through AIDS education programs (Figure 4a). The overall rate dropped by 14% between 1985-86 and 1986-87. In 1987, infections in the 15- to 29-year-old group represented 78% of all cases of reported gonorrhoea in Canada (Figure 4b). The infection rate in women between 15 and 19 years of age is twice that of men in the same age group. Part of the greater decrease in incidence of gonococcal infection in men may be related to behavioural changes in the homosexual population due to AIDS education.

In 1987, 72 children were reported to be infected in Canada. In children under 10 years of age, excluding those who may have acquired gonococcal infection at birth, infection with *N. gonorrhoeae* is suggestive of child abuse.



The efficiency of transmission is related to frequency of exposure as well as site of infection. The estimated frequency of female to male transmission is 20% after one exposure, but increases from 60% to 80% after four exposures (Holmes et al. 1970). Approximately 50% to 90% of women who are sexual partners of infected men acquire the infection.

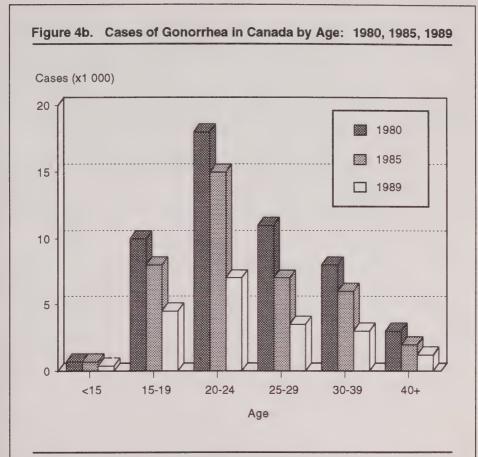
The rate of asymptomatic carriage is not known. The production of symptomatic disease may relate to the infecting strain. Asymptomatic carriers are important contributors to the spread of disease in the population.

Of concern now is the rapid rise of antibiotic-resistant strains of N. gonorrhoeae, especially among high-risk groups (Yeung et al. 1991).

Clinical Manifestations

N. gonorrhoeae causes gonorrhoea and related clinical conditions such as urethritis, cervicitis, and conjunctivitis, and is associated with chronic sequelae of PID, arthritis, and epididymitis. The incubation period is from two to seven days. Infections may also occur at other mucosal sites such as the throat and rectum. Systemic or disseminated infections can involve





P.R. Gully and D.K. Rwetsiba, "Trends in Gonorrhea in Canada: 1980-1989," Canada Diseases Weekly Report 17 (25 May 1991), 109.

the skin and joints, and can occasionally cause endocarditis or meningitis. Babies born to infected mothers may acquire an eye infection called ophthalmia neonatorum.

Co-infection with C. trachomatis is common (20% to 30% of symptomatic men and 30% to 50% of women). People with both infections are more likely to develop PID than those with either infection alone (Bowie et al. 1981; Paavonen et al. 1986).

Links to Infertility

The relationship between gonococci, PID, and tubal infertility was first reported in the pre-antibiotic era (Noeggerath 1876; Brandt 1985). Gonorrhoea is probably responsible for 20% to 40% of all PIDs caused by exogenous sexually transmitted pathogens. Gonococcal PID is usually symptomatic; thus, it is often diagnosed and treated before progression to long-term sequelae such as ectopic pregnancy or tubal infertility. The outcome of treated gonococcal PID is more favourable with regard to fertility compared to that of non-gonococcal PID (Brunham et al. 1988).

The frequency of PID in women with concomitant chlamydial and gonococcal infections is increased (Bowie and Jones 1981); however, the mechanism for this synergistic interaction is not clear. Tissue damage by gonococci in the upper genital tract may allow invasion by other microorganisms, especially by anaerobic bacteria normally resident in the vagina, and cause tubo-ovarian abscesses.

N. gonorrhoeae possesses many mechanisms to counteract host defences to cause both localized and systemic infections. It is able to adhere strongly to the mucosal surfaces of the urethra without being washed away through a protein on its outer membrane (protein II) and by appendages called pili. Pili also allow the gonococci to resist being ingested by host white cells. To evade host immune responses, N. gonorrhoeae is able to generate (1) mutations of its outer membrane structures pili, protein II, and lipoligosaccharide; (2) protein III, a protein to which the host generates antibodies that block normal serum bactericidal activity; (3) a protease capable of clearing host IgA antibody response on the mucosal surface; and (4) resistance to normal bactericidal activity in host serum.

To cause disseminated disease, gonococci attach to non-ciliated cells and are gradually enveloped by the host epithelium. Once inside the host cell, they are able to resist intracellular host defences and multiply. Eventually, the gonococci exit from the basal surface of the cell and invade the bloodstream. Protein I enables the gonococcus to injure the host cell membrane, but it has not been shown that blocking of protein I with antibodies can prevent tissue damage.

The gonococci produce a variety of enzymes and structural components that can cause tissue damage in the host. They include the lipoligosaccharide and peptidoglycan, which interfere with ciliary action of fallopian tubes in culture.

Adverse Pregnancy Outcome

Gonococcal infections in pregnancy have been correlated with septic abortion, premature membrane rupture, and prematurity. The newborn is at increased risk of acquiring gonococcal infections following premature membrane rupture.

Neonatal Infections

Gonococcal conjunctivitis in infants may cause permanent corneal damage if untreated or if treatment is delayed. The disease may also spread systemically and cause pharyngitis, meningitis, or arthritis. Overwhelming sepsis can be fatal.

Diagnosis

The methods, rates of sensitivity and specificity, and estimated costs of laboratory diagnosis of gonococcal infection are shown in Table 6.

Table 6. Laboratory Diagnosis of Gonococcal Infections

Method	Specimen	Sensitivity (%)	Specificity (%)	Cost (\$)
Microscopy (gram-stained smear)	urethral swab cervical swab	90 70	95 80	3.00
Culture	both swabs	85-98	98-100	10.00
Antigen detection*	both swabs	70-90	80-95	10.00
Gene probe	both swabs	90-95	99	15.00

^{*} Rectal or pharyngeal specimens are not suitable for gonococcal antigen detection tests, as false positives may arise from other *Neisseria* species present.

Interventions

Treatment

The use of penicillin in the 1940s greatly reduced the incidence of gonococcal infections; however, its widespread use gradually led to the emergence of resistant mutants that are the major cause of gonorrhoea in different parts of the world. Gonococci are able to mediate high levels of antibiotic resistance through mutations both in their own genes and in the plasmids to which they are host. In recent years, resistance to tetracycline has also become common. The current recommended drugs for gonococcal infections are ceftriaxone and spectinomycin. Over 99% of infected individuals will be cured.

The use of silver nitrate in the eyes of newborns has reduced the risk of ophthalmia in babies born to infected mothers from 30% to 0.5%.

Vaccine

Most vaccine studies have concentrated on the use of pili as antigens to stimulate protective immune responses; however, the protection is at best partial even with homologous strains. A broadly reactive polyvalent antigen preparation may offer better protection but would still be subject to future gonococcal antigenic variation in the bacterial population.

As the role of various outer membrane proteins becomes clearer, the use of genetically expressed protein I, which will have no contaminating traces of protein III, may offer a viable alternative to pili vaccines. Antibodies to protein I have been shown to protect against re-infection.

Prevention

Primary prevention using well-developed educational programs for youth and for sexually active adults is the foundation on which all other programs should be established. In addition, programs to screen women at increased risk; to identify the asymptomatic reservoir and treat infections; to identify and treat male contacts; and to identify, screen, and treat high-frequency transmitters can all reduce the incidence of gonococcal infection in communities.

No vaccine is likely possible for the next five years. However, other programs are effective in many countries, and it should be possible in Canada to reduce gonococci at least tenfold over the next five years.

Research Priorities

Research into N. gonorrhoeae should be a priority in several areas:

- Operational and epidemiologic studies should be done to identify, treat, and educate those people contributing to the reservoir of N. gonorrhoeae in Canada.
- Studies should be conducted on bacterial pathogenesis to determine the factors by which organisms cause disease.
- Continuing efforts should be made to identify bacterial components that could be effective if used as a vaccine in immunization programs.
- Studies should be undertaken to determine the interactions of gonococci with *C. trachomatis* and the role of each pathogen in acute and chronic diseases in the upper female genital tract.

3. Treponema pallidum

Introduction

Treponema pallidum, the causative agent of syphilis, is a spirochete that has never been successfully cultivated *in vitro*; therefore, knowledge about the biology of the organism is deficient. Studies are usually conducted in rabbit testes. It is almost exclusively sexually transmitted because it is susceptible to desiccation, which limits spread by fomites or clothing.

Epidemiology

Syphilitic infection has been on the decline worldwide since the introduction of penicillin therapy (Figures 5a-5c). However, syphilis has re-emerged in adults in the major cities of many industrialized countries, including Canada. For example, rates rose from 8.6 per 100 000

population in 1986 to 9.3 per 100 000 population in 1987, especially in women of childbearing age who have limited access to the health care system (Canada, Health and Welfare Canada 1989; Rolfs and Nakashima 1990). In particular, the exchange of sex for drugs, specifically cocaine. seems to be responsible for much of the epidemic. Women addicted to cocaine who acquire syphilis and have subsequent pregnancies often do not receive prenatal care. Congenital syphilis is becoming more common in some American urban ghettos.

Since syphilis is recognized as a co-factor in HIV acquisition, two major problems emerge: (1) the spread of HIV is accelerated in high-risk groups; and (2) the treatment for syphilis is inadequate in HIV-infected individuals who may have accelerated progression or an atypical clinical manifestation.

Illustrative Case — Don't Forget About Syphilis

Diane is a 28-year-old woman who has just completed her third pregnancy. Previously, she had two therapeutic abortions for first-trimester pregnancies. She also briefly experimented with intravenous drugs for two years and recalls about eight or nine sexual partners in her lifetime. She currently is in a stable relationship and planned her current pregnancy.

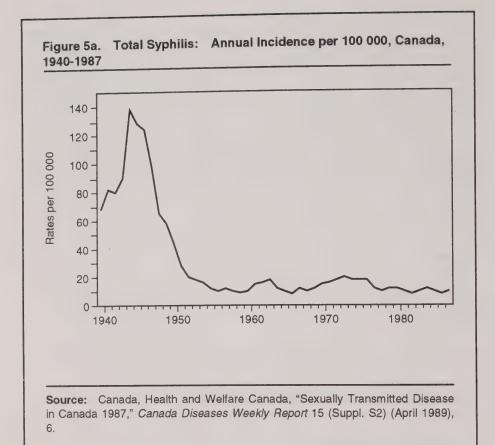
For several reasons she is unhappy with the health care professions and intended to have this pregnancy and deliver at home using "natural" means without any medical help during pregnancy or birth.

The pregnancy proceeded normally until about the 36th week. At that time she noticed an absence of fetal movements. Within 24 hours she had uterine contractions and presented herself to the hospital emergency room. Her cervix was partially dilated. Within an hour she delivered a macerated stillborn.

Laboratory studies disclosed a VDRL of 1:64. She recovered uneventfully and has been treated with 2.4 million units of benzathine penicillin.

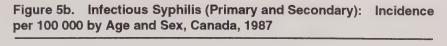
Learning Points

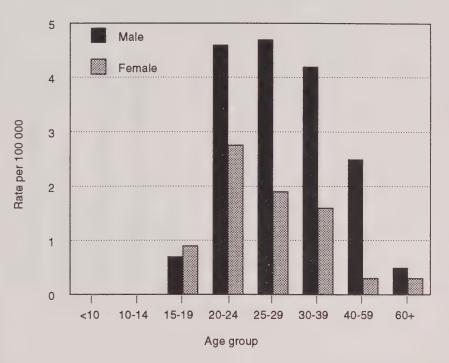
- Syphilis is currently undergoing a resurgence in some industrialized countries. Women and their caregivers need to know that there is a continuing risk of syphilis and that it has severe consequences during pregnancy, including congenital infections.
- The most effective way to diagnose this illness is through continued widespread use of syphilis screening in early pregnancy.
- Treatment in early pregnancy usually prevents complications of stillbirth, premature labour, and congenital malformations.
- Screening tests were not done for other STDs, particularly N. gonorrhoeae, C. trachomatis, and HIV. This individual is at increased risk and should be offered care and counselling.



Treponemes are transmitted directly from an infected host to a sexual partner during primary or secondary stages, when the organism passes from the lesion of one partner to the other through a skin abrasion. Between 30% and 50% of partners are infected after unprotected intercourse.

Transmission to the fetus is also a major route of spread. It can occur during the primary and secondary infection stages and for up to eight years during the period of latency when no disease is present. In a prospective study of untreated syphilis from 1890 to 1910, Gjestland (1955) observed that 26% of babies born to syphilitic women are free of disease or recover spontaneously, 25% acquire antibodies but remain clinically well, and 49% show signs of disease.





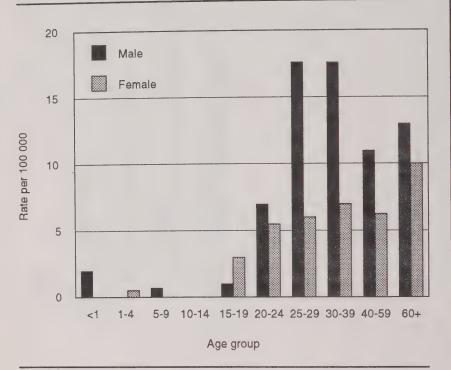
Source: Canada, Health and Welfare Canada, "Sexually Transmitted Disease in Canada 1987," Canada Diseases Weekly Report 15 (Suppl. S2) (April 1989), 7.

Clinical Manifestations

Primary Syphilis

After successful penetration of the host, the organism will multiply at the entry site (genital mucosa or skin) within five hours. A primary lesion will appear over the next 10 days and it will gradually enlarge to form an ulcer about 1 to 2 cm in diameter. Skin lesions can be found on the eyes, nose, and genital area. Bone lesions are found in congenital syphilis.

Figure 5c. Latent and Other Syphilis: Incidence per 100 000 by Age and Sex, Canada, 1987



Source: Canada, Health and Welfare Canada, "Sexually Transmitted Disease in Canada 1987," *Canada Diseases Weekly Report* 15 (Suppl. S2) (April 1989), 8.

Secondary Syphilis

After an interval of two to six weeks, often as the primary ulcer is healing, a generalized or secondary stage of infection occurs. At this time, treponemes spread throughout the body. The skin is usually involved, but other organs, including the liver, kidney, and meninges, can also be involved. A rash, swollen lymph glands, and mucous patches may be present. Without treatment, the disease becomes latent due to the body's immune response. Although treponemes are still present, no disease is evident. Organisms can cross the placental barrier at this stage.

Tertiary syphilis can have many manifestations, including psychosis and neurologic illness, and can involve organs such as the heart (e.g., cardiac failure). There can be extensive tissue damage to the cardio-vascular system, bone, brain, skin, and internal organs, and chronic progressive destruction of nerve fibres in the spinal cord. The mechanism by which *T. pallidum* invades the host tissues and the central nervous system is unknown. Experiments by Thomas et al. (1988) showed that the spirochete can penetrate cells and be found in the cell junctions. Infection brings on a rapid and vigorous immune response from the host, but in the secondary stage the response is moderated, resulting in a latent stage of infection that may last for decades. Persistence of the organism in the body without evoking host immune is unexplained.

Congenital Syphilis

Lesions of the skin, mucous membranes, bone, liver, and placenta may be present. These are due to vasculitis, necrosis, and fibrosis. At autopsy, bone lesions are found in 97% of infants less than six months of age.

Ninety-five percent of primary or secondary syphilis in pregnancy will result in fetal infection (Chawla et al. 1988).

Infection of the fetus with *T. pallidum* usually occurs at about 16 to 20 weeks of gestation. As a result, programs to diagnose and treat syphilis in early pregnancy can be effective.

Late congenital syphilis is associated with mental deficiency, chronic meningitis, blindness, and deafness. Many organ systems can be involved with *T. pallidum* infection, including the teeth, bones, nervous system, cornea, cochlea, and skin. Although many infants die in the neonatal period, others live into adulthood, albeit with a variety of disabilities.

Links to Infertility

Harman (1917) studied 150 women with syphilis and 150 healthy women, both of similar social status. No impairment of fertility was found in women with syphilis.

Adverse Pregnancy Outcome

The risk of prematurity, perinatal death, and congenital syphilis is related directly to the particular stage of disease in the mother during pregnancy. Fiumara et al. (1952) reviewed 59 cases of women with untreated primary or secondary syphilis; 50% delivered infants with congenital syphilis; and 50% of births were premature or stillborn. Early latent syphilis is associated with decreased incidence of congenital syphilis and perinatal morbidity compared to primary or secondary syphilis. In late latent syphilis, 10% of babies acquire syphilis, and 9% to 11% are stillborn or premature.

Spontaneous abortion during the second and third trimesters (peaking at about eight months) occurs in about 10% of infected patients, stillbirths

in about 20%, and premature labour with perinatal death in an additional 20%; most of the remainder survive but have congenital syphilis.

In Africa, where 5% to 19% of miscarriages are attributed to syphilitic infections, women seropositive for syphilis are five times as likely as controls to have an abortion or stillbirth. Beyond 12 weeks of gestation, 50% of syphilitic women will have spontaneous abortions as opposed to 15% in healthy women (Guinness et al. 1988).

Diagnosis

Clinical Diagnosis

Primary syphilis must always be excluded whenever genital ulceration is observed. Ulcers are classically indurated, elevated, and not painful. Secondary and tertiary syphilis can mimic many diseases and have to be considered in patients with a wide variety of presentations. Congenital syphilis can also mimic other infections in the newborn.

Laboratory Diagnosis

The laboratory diagnosis of syphilis can be made by the detection of treponemes in the primary chancre or in secondary lesions. Failure to find the organism does not exclude a diagnosis of syphilis due to the low sensitivity of darkfield microscopy, especially if the patient had been treated. Serum antibodies can be detected one to four weeks after the primary chancre has formed. A positive result with a non-specific assay such as rapid plasma reagin (RPR) or Venereal Disease Research Laboratory tests for serologic diagnosis of early syphilis should be confirmed by *T. pallidum* haemagglutination assay to exclude false-positive reactions with non-treponemes. After effective treatment, 72% and 56% of patients with first episodes of primary or secondary syphilis became seronegative by RPR within 36 months (Romanowski et al. 1991). A negative serologic test does not preclude a past history of syphilis.

Interventions

Treatment

Historically, treatment with arsenicals prevented neonatal syphilis. Penicillin is 98% effective in preventing congenital syphilis in babies born to infected women. Long-acting penicillin is the treatment of choice for all patients with *T. pallidum* infection unless they are allergic. Although penicillin is probably less effective in patients infected concurrently with HIV and *T. pallidum*, no other regimens have been proven to be superior. Ceftriaxone is efficacious but needs further evaluation. Erythromycin therapy for women allergic to penicillin will result in a 10% to 30% failure rate because fetal blood level attained is only 6% to 20% of maternal serum concentration.

Tetracycline is effective, but not recommended for use during pregnancy because of liver toxicity, dental staining, and enamel hypoplasia.

Method	Specimen	Sensitivity (%)	Specificity (%)	Cost (\$)
Microscopy (darkfield)	lesion	60-90*	90	16.00
Antigen detection	lesion	80-90	100	8.00
Serology:** VDRL/RPR MHA-TP FTA-AB	blood	80-99 82-100 98-100	98 99 98	6.00

- * Sensitivity depends on the age of the lesion.
- ** Serologic testing is the only method for testing non-infectious syphilis.

VDRL (Venereal Disease Research Laboratory) and RPR (rapid plasma reagin) tests are based on reaction of syphilitic antibody to lipids and are thus non-specific tests for treponemes.

MHA-TP (microagglutination assay for antibodies to *T. pallidum*) and FTA-AB (fluorescent treponemal antibody absorption) tests detect treponemal specific antibodies in the blood of patients using *T. pallidum* carried on sheep red blood cells or fixed on glass slides.

The timing of therapy is critical. Treatment of women early in pregnancy (first trimester) is almost totally effective in preventing congenital syphilis (Zenker and Rolfs 1990).

The treatment failure seen in 1% to 2% of women may be due to (1) fetus diseased and close to abortion; (2) women re-infected before delivery; and (3) treatment within two weeks of delivery. Current maternal therapy may be inadequate to treat *in utero* syphilis in the third trimester (Rawstron and Bromberg 1991). Infected infants born to mothers infected late in pregnancy may be asymptomatic at birth. They should be treated if routine follow-up cannot be assured.

Prevention

Primary prevention strategies should be effective in reducing the incidence of *T. pallidum* infection. Secondary prevention is a continuing priority. All patients at risk of STDs should be tested for syphilis, and those with positive serology should be treated and followed up to ensure cure. This approach should ensure that tertiary syphilis remains a rare disease in Canada and should prevent most congenital syphilis. Failures of prevention include faulty public health procedures or clinical judgment. In 30% to 60% of cases, failure is due to a delay in prenatal care (i.e., too late to prevent congenital syphilis in third trimester). Lack of prenatal care is the leading reason for failure to prevent congenital syphilis.

Control Strategies

Continuing effective strategies to decrease the incidence of syphilis in Canada are needed. They include:

- treatment of primary and secondary cases and case detection through partner referral (aimed at reducing reservoir of disease);
- follow-up of seropositive patients (reactor follow-up); and
- routine prenatal screening because it is more effective than premarital screening (rescreening of women at risk near term is necessary because syphilis may be acquired during pregnancy).

Research Priorities

Research priorities for T. pallidum include:

- identification of protective antigens that may evoke specific cellular immunity and improve serologic diagnosis;
- further studies to understand the mechanism of latency and pathogenesis of the various manifestations of syphilis infection; and
- epidemiologic studies and control programs to permit the eradication of this pathogen from Canadian society through the identification and treatment of reservoirs and ensuring all avenues of transmission are effectively curtailed.

4. Haemophilus ducreyi

Introduction

Chancroid is an ulcerative sexually transmitted illness due to *Haemophilus ducreyi*. It is receiving increased attention as a more important condition due to its role in facilitating transmission of HIV.

Epidemiology

Haemophilus ducreyi is the etiologic agent of chancroid (genital ulcer disease). Chancroid is sexually transmitted and is more prevalent in lower socioeconomic groups. Men, especially uncircumcised men, are more susceptible to infection than women (ratio 10:1). In many developing countries, chancroid may be the second or third most prevalent STD (Ronald and Albritton 1990). Incidence in the United States and Canada has decreased in recent years, with only sporadic epidemics in which prostitutes are usually identified as the reservoir of disease (Hammond et al. 1980; Schmid et al. 1987).

Clinical Manifestations

The incubation period of *H. ducreyi* is three to seven days. Trauma or a break in the skin is probably essential for infection, which results in the development of genital ulcers that can be painful and bleed easily. Acute inflammations of lymph nodes develop into bubos (tender, enlarged, and

inflamed lymph nodes, particularly in the axilla or groin), which, if untreated, will develop into abscesses. The infection may persist for months if untreated.

Links to Infertility

No links to male or female infertility have been shown, nor has *H. ducreyi* been shown to cause disease in infants born to infected mothers. However, the presence of genital ulcers has been shown to be a risk factor for the acquisition of other STDs, especially HIV (Plummer et al. 1991).

Diagnosis

Table 8 shows the diagnostic methods for H. ducreyi.

Table 8. Laboratory Diagnosis of Haemophilus ducreyi Infection

Method	Specimen	Sensitivity (%)	Specificity (%)	Cost (\$)	Comments
Culture	ulcer	80	100	12-15	
Antigen detection	ulcer	n.a.	n.a.		research only
Serology	blood	n.a.	n.a.		research only

n.a. = not available.

Interventions

Treatment

The current recommended treatment is erythromycin, since most strains of H. ducreyi have developed resistance to penicillin, tetracycline, trimethoprim, and sulfonamides. Third-generation cephalosporins, ciprofloxacin, and azithromycin are effective alternatives. Patients co-infected with HIV often fail to respond as well to therapy.

Vaccine

Virulence factors have not been identified. Despite clinical cure, the disease recurs with re-exposure; thus, the antibody response to infection and its significance in protection from re-infection are not clear.

Prevention.

In spite of the low incidence of disease in Canada, prevention and control strategies for *H. ducreyi* are important because of its links to HIV-1 transmission. Recent outbreaks in Canada and the United States have been effectively controlled by the widespread treatment of core transmitters, such as prostitutes who may continue sexual activity despite genital ulceration.

An effective program for monitoring target populations should consist of encouraging condom use, regular pelvic examination, early treatment of lesions, and partner/contact tracing.

Research Priorities

Priorities for research in H. ducreyi include:

- improved technology to diagnose *H. ducreyi* by methods other than culture;
- understanding the disease pathogenesis of both ulcers and bubos; and
- further studies of the links to HIV infection.

5. Mycoplasmas and Ureaplasma

Introduction

Mycoplasmas are the smallest micro-organisms capable of self-replication on artificial media. They lack a rigid cell wall and require sterols for growth. Ureaplasmas form tiny colonies (called T-strain mycoplasmas) that rapidly break down urea to ammonia. Mycoplasma species that are pathogenic for humans include Mycoplasma pneumoniae, the cause of atypical pneumonia; Mycoplasma hominis, Mycoplasma genitalium, and Ureaplasma urealyticum are associated with genitourinary infections.

Epidemiology

Mycoplasmas were thought to be normal flora of the genitourinary tract because they can be isolated from as many as 50% of normal sexually experienced adults (Glatt et al. 1990). The evidence for sexual transmission came from studies that showed increased mycoplasma and ureaplasma colonization after puberty with increasing number of sexual partners. Sexually mature people who are not sexually active are less frequently colonized (McCormack et al. 1972). In a study in Halifax, Nova Scotia, *M. hominis* was isolated from 35.5% and 39.7% and *U. urealyticum* from 72% and 75% of women attending family-planning clinics and prenatal clinics, respectively (Embil and Pereira 1985). These prevalence rates are similar to those reported in the United States.

Up to 45% of infants born to mothers with mycoplasmas in the genital tract are colonized at birth, but such colonization does not usually persist and is not usually associated with illness in the infant. Direct transmission in utero is unlikely, as babies delivered by Caesarian section have a lower frequency of colonization.

Clinical Manifestations and Links to Infertility

U. urealyticum is implicated in non-gonococcal urethritis, PID, and possibly adverse pregnancy outcome (Bowie et al. 1978; Cates and Wasserheit 1991). Post-partum fever is often due to *M. hominis*. The

following clinical manifestations have putative correlations with infection and links to infertility.

Male Infertility

Mycoplasmas have been suggested to reduce male fertility by inhibiting sperm production, causing formation of abnormal sperm, reducing sperm motility, or impairing the passage of sperm (Taylor-Robinson 1986; Swenson et al. 1979). Evidence for these associations requires further study.

Tubal Factor Infertility

No direct evidence shows a causative role to tubal infertility due to PID. In a study of 88 couples with primary infertility, conception was not improved in women treated for mycoplasmas (Harrison et al. 1975). However, serological evidence shows that antibodies to *M. hominis* occur three times (36%:11%) more often in women with tubal infertility than in women with other reasons for infertility (Miettinen et al. 1990).

Adverse Pregnancy Outcome

In a prospective study of 801 women with cervicitis (Investigators of the Johns Hopkins Study 1989), M. hominis was found to be associated with pre-term delivery (odds ratio = 2.0, 90% confidence limits 1.42-2.93). Other correlations in which their causal role is uncertain include fever following vaginal delivery, spontaneous abortion or stillbirth, and low birthweight.

Diagnosis

Laboratory Diagnosis

Because of the lack of mycoplasmal culture facilities, cultures for mycoplasmas are not routinely done.

Growth of *M. hominis* and *Ureaplasma urealyticum* usually requires three to seven days of incubation, while *M. genitalium* takes more than two weeks for colony formation. Culture is the only means to make a diagnosis.

Interventions

Treatment

Tetracycline is indicated for mycoplasma infections, if evidence supports its role as a pathogen. Patients unresponsive to tetracycline may have resistant strains and should be treated with erythromycin (Møller et al. 1990).

Vaccine

No vaccine has been developed.

Prevention.

The use of barrier contraceptives decreases the likelihood of colonization.

Studies on the use of erythromycin for pregnant women with ureaplasma suggest that treatment during the third trimester may prevent chorioamnionitis and low birthweight in some populations (McCormack et al. 1987). Further studies are needed before making this a general recommendation.

6. Trichomonas vaginalis

Introduction

Trichomonas vaginalis is a parasite that causes infections of the vagina in women and rarely infections of the urethra and possibly prostate in men.

Epidemiology

Estimated annual incidence in the 1970s was 180 million cases worldwide and 2.5 to 3 million women infected in the United States (Hammill 1989). Between 8% and 35% of STD clinic attendees are infected. In 1983-85, 7.3% of 247 women attending a STD clinic in Halifax, Nova Scotia, were infected with *T. vaginalis* (Pereira et al. 1990). Prevalence generally increases with sexual activity and the non-use of barrier methods of contraception.

Transmission is predominantly sexual. In rare circumstances, non-sexual transmission is possible; it presumably can be transmitted by contaminated fomites such as towels, because it can survive in or on moist objects for several hours.

Clinical Manifestations

The incubation period of *T. vaginalis* is 3 to 28 days. Most (50% to 70%) infected women present with discharge and itching. The vagina, and sometimes the cervix, are inflamed.

Most men with trichomonal infections are asymptomatic. The most common site of asymptomatic infection is the urethra, although the organism has been isolated from epididymal aspirates and prostatic fluid. Infected men rarely present with watery or white discharge from the urethra.

Links to Infertility

- Trichomoniasis is present in 3% of asymptomatic women attending infertility clinics, but no late sequelae of infection are known (Rein and Chapel 1975).
- Male infertility: *T. vaginalis* can survive in semen. This may have implications for transmission through artificial insemination (Daly et al. 1989). Evidence is conflicting as to whether it affects sperm viability or mobility through changing semen viscosity (ibid.; Gopalkrishnan et al. 1990). Trichomonads have been isolated from 10% of infertile men, but the significance of the association is not known.

Diagnosis

Table 9 shows the methods of detection and other factors associated with the laboratory diagnosis of *T. vaginalis*.

Table 9. Laboratory Diagnosis of *Trichomonas vaginalis* Infections

Method	Specimen	Sensitivity (%)	Specificity (%)	Cost (\$)
Wet mount	genital secretions/discharge	60-75	75	3.00
DFA	genital secretions/discharge	70-86	70-75	7.00
Culture	85-97%	80-90	100	15.00

Rapid non-culture tests such as latex agglutination and direct fluorescence assays provide rapid diagnosis with sensitivity and specificity approaching those of culture, but these are not widely available.

Interventions

Treatment

A single oral dose of metronidazole is efficacious for trichomoniasis, with cure rates of 95%. Some physicians routinely prescribe a seven-day course of treatment to achieve higher cure rates.

Vaccine and Research

Little is known about the mechanisms whereby *T. vaginalis* causes disease. In women, symptoms appear or become worse during or after a menstrual period, suggesting that changes in the vagina may affect pathogenicity.

Local antibodies have been reported in over 50% of women with infection. Repeated infections are common; thus, protective immunity may not occur after infection.

Prevention

Asymptomatic men are an important reservoir of disease. Control strategies should include effective treatment of infected men and women.

7. Human Herpes Viruses (Herpes simplex) Types 1 and 2

Introduction

Six human herpes viruses have been recognized, each of which appears to be well adapted to its hosts and thus is harboured by a significant portion of the population. Of these, herpes simplex virus types 1 and 2 (HSV-1, HSV-2) will be discussed together, as their biological

properties and clinical manifestations are similar and are often not differentiated in clinical diagnoses. HSV-1 is the usual cause of oral, facial, and eye lesions and sometimes neurologic infection. However, 7% to 35% of genital lesions can be due to HSV-1. HSV-2 causes genital lesions but also can be found in lesions elsewhere and in infected newborns. HSV-2 is more likely to recur than HSV-1.

Epidemiology

In Canada, a dramatic increase has occurred in the number of laboratory reports of herpes virus infections since 1978 (Figure 6). This trend is partly a reflection of increased access to testing since the late 1970s. The number of reports in 20- to 29-year-olds represents 53% of the total in 1987. Two-thirds of all such infections are in women. In Canada in 1982, 1 of 3 500 babies born alive developed neonatal herpes. In the United States, genital herpes increased tenfold and neonatal herpes increased fourfold from 1966 to 1981. In both countries, 80% of patients with a first episode of genital HSV were between 18 and 36 years of age.

Clinical Manifestations

Primary Infection

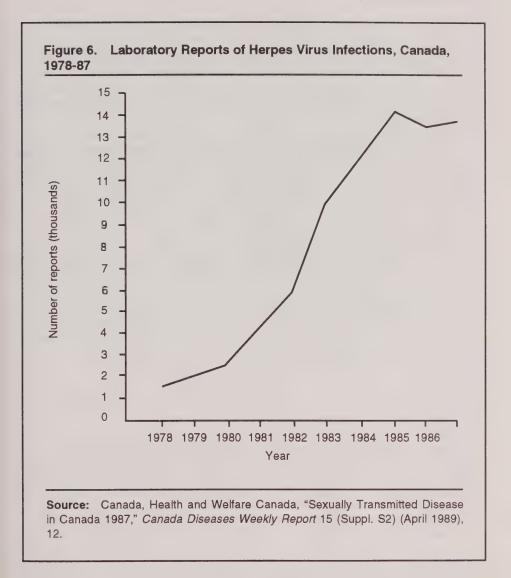
Exposure of mucosal surfaces or abraded skin allows for viral entry. The incubation period is 6 to 8 days (range 1 to 26 days). The virus multiplies at the site of entry and produces symptoms of fever, swollen glands, headache, malaise, and pain. For genital infections, there may be ulcerative lesions accompanied by pain, itching, and vaginal or urethral discharge. The lesions run a two-week course, peaking at 8 to 10 days. Virus is shed for 12 days. Clinical manifestations include cervical inflammation (90%), dysuria (80%), blood in the urine, and pelvic pain as well as urinary retention. Among individuals with extra-genital complications, pharyngitis (13%), aseptic meningitis (36%), and nervous system dysfunction (2%) are the most common.

Latent Infection

As the primary infection subsides, the virus migrates to nerve cells in sensory ganglia from the nerve cells in the skin. The virus is maintained in a largely repressed non-infectious state so that the host cell is able to continue normal activities. All primary herpes simplex viruses seem to result in latent infection.

Reactivation or Recurrent Infections

Under certain conditions in the host, which are yet to be defined, infectious virus is reactivated and returns to the inoculation site via peripheral sensory nerves and then replicates to produce lesions. The reactivation rates for HSV-1 and HSV-2 genital infections are 14% to 25% and 60% to 88%, respectively. Twenty-five percent of recurrent genital herpes occur with symptoms. The appearance of lesions depends on the amount of virus at the local site, viral-host cell interactions, and the ability



of the host to suppress replication. The amount of virus shed and the duration of infection are usually reduced on recurrences, suggesting that primary infection elicits protective immune responses in the host.

Links to Infertility

HSV-1 and HSV-2 have not been found to be linked to tubal infertility. Pregnancy did not alter the frequency of recurrence in three studies that assessed 500 pregnant women, of whom 14% had clinical recurrence at term. The stage of pregnancy does not alter the frequency of virus isolation. In six studies of over 27 000 asymptomatic women, the frequency of isolation was 0.09% to 0.32% (Brown et al. 1985).

Herpes simplex virus is not prone to cause spontaneous abortion, prematurity, or intrauterine infection. Nahmias et al. (1971) reported that 5 of 9 women (54%) with primary herpes at less than 20 weeks of gestation had spontaneous abortions, compared to 7 of 28 women (25%) with recurrent infection.

Congenital infection is rare. Approximately 50% to 80% of infants exposed to a primary maternal herpes simplex virus infection during vaginal delivery become infected; this rate decreases to 2% to 5% in recurrent infections. The high attack rate in primary infection may be due to the presence of large amounts of virus, the presence of maternal cervical infections, or the absence of maternal antibodies in the newborn. In a collaborative anti-viral treatment study conducted by the National Institute of Allergy and Infectious Diseases (Hutto et al. 1987) of neonatal herpes caused by HSV-2, 13 of 192 infants acquired herpes simplex virus perinatally. Of these, 2 died, 10 had serious sequelae, and 1 became blind. In a study of 29 women with herpes in pregnancy by Brown et al. (1985), 6 acquired a first episode of genital herpes, and all of their infants showed severe consequences of prematurity, intrauterine growth retardation, or neonatal herpes simplex virus infection. None of the infants born to mothers with non-primary infections had perinatal illness.

Diagnosis

The laboratory diagnoses of HSV-1 and HSV-2 infections are shown in Table 10.

Method	Specimen	Sensitivity (%)	Specificity (%)	Cost (\$)
Culture	lesion	60-80	90-98	20.00
Microscopy	lesion	60	50-60	7.50
Antigen detection	lesion	60-80	70-80	7-10.00
Gene probe	lesion	90-99	90-99	15.00

Interventions

Treatment.

Anti-viral agents that most closely resemble the structure of viral DNA but are not functional when incorporated interfere with viral replication. Acyclovir is efficacious against herpes simplex virus. Studies to evaluate the use of acyclovir therapy for pregnant women and for infants exposed to herpes simplex virus at delivery are under way. Research is ongoing for agents that may block viral attachment or entry into host cells or prevent the establishment of latency.

Prevention

Shedding of herpes simplex virus at delivery is an important mechanism of transmission to the newborn, and the risk to the neonate is greatest if the mother is experiencing a first primary genital infection at the time of delivery. The difficulty in preventing transmission or identifying infants at risk lies in the fact that thus far studies have shown that most infants with neonatal infection were born to mothers without a history of genital herpes. Shedding at delivery should therefore be considered as likely in asymptomatic women with no history of HSV infection as in women with a history of infection (Prober and Arvin 1989). Asymptomatic viral shedding is estimated to occur about 1% of the time. Serial prenatal cultures for genital HSV in pregnant women are currently not recommended, since they fail to predict asymptomatic shedding at delivery, even in women with recurrent genital infections.

Viral culture is recommended for verifying whether shedding has ceased in women with clinically evident genital infection during pregnancy. A decision regarding the mode of delivery can then be made on the basis of culture result prior to delivery, the presence of lesions on external and internal examination, and signs and symptoms at the time of delivery. Caesarian delivery should not be considered merely as a precautionary measure for women without signs of an active infection at delivery.

For women with a past history of genital infection, a culture obtained at delivery may help to identify infants at risk of HSV infection, but more studies are needed to establish its usefulness.

Infants exposed to HSV at delivery should have cultures from the eyes, throat, stool, and cerebral spinal fluid and be closely monitored for signs of infection for four to six weeks. Intravenous acyclovir should be given only if the infant is culture-positive. There are insufficient data at present on the safety and efficacy of acyclovir to recommend its use as a prophylactic measure either for a woman infected in pregnancy or for an exposed infant. Acyclovir may reduce symptomatic illness or rate of recurrence, but asymptomatic shedding may still occur.

Vaccine and Research Priorities

A vaccine for herpes simplex virus infection should reduce the severity of disease and lower the frequency of latent infections established after the primary infection. However, a live attenuated vaccine may establish latency. Subunit vaccines that induce neutralizing antibodies to various glycoproteins on the outer membrane of the virus have been tried in human subjects without proven success.

Between 20% and 40% of young adults have antibodies to herpes viruses. Immunity to HSV-1 confers some protection against HSV-2. Immunity shortens shedding and the duration of pain. There are usually fewer lesions, a lower frequency of systemic symptoms, and a shorter healing time. A better understanding of the role of immunity in the pathogenesis of herpes virus infections is needed for more effective vaccine formulation.

Rapid and sensitive methods to detect asymptomatic infections in pregnancy are needed to decrease the incidence of neonatal HSV infections.

8. Cytomegalovirus

Introduction

Cytomegalovirus (CMV) is one of the herpes viruses. Worldwide, it is the most common cause of congenital viral infection of the fetus, with an incidence of 0.2% to 2.2% among live births. Cytomegalovirus is also recognized as the most frequent infectious cause of mental retardation.

Epidemiology

Cytomegalovirus infections are endemic throughout the world. Their prevalence and incidence are correlated with age, socioeconomic background, breast feeding, and sexual activity.

A Canadian study showed that the prevalence of cytomegalovirus infection in a STD clinic population of 247 women was significantly correlated with young age (12.6% in 14 to 22 years of age versus 2.9% in \geq 23 years of age) (Pereira et al. 1990). In the United States and Great Britain, the prevalence of antibodies to cytomegalovirus is 40% to 60% in adults of middle to upper socioeconomic status compared to 80% in those of lower socioeconomic status (ibid.).

Transmission

The modes and risk of transmission of cytomegalovirus are shown in Table $11. \,$

In normally immunocompetent infants or adults, cytomegalovirus rarely causes disease, but in immunocompromised individuals, disease can be severe; thus, pathogenesis must be related to host factors. Like all herpes viruses, cytomegalovirus can remain latent in tissues after a primary acute infection. Unlike herpes simplex, which remains latent in neural cells, latent cytomegalovirus can be found in organs such as the kidneys and liver, and in cervical tissue, salivary glands, semen, and circulating white blood cells.

Maternal immunity fails to prevent the reactivation of infection or transmission. However, it provides partial protection against damaging sequelae in the neonate. In a cohort of infants infected at birth (125 from primary CMV and 64 from recurrent infection), 15% and 13% of infants whose mothers had primary CMV had mental impairment and hearing loss, respectively, compared to 0% and 5% in the recurrent infection group (Fowler et al. 1992). In infected infants, antibody response begins at 4 to 18 weeks, with heavy shedding of virus. Symptomatic infants may have defects in antibody or cellular immunity response to viral infection. Circulating immune complexes and autoimmune responses may play a role in immunopathologic damage seen in infants with severe infections.

Table 11.	Transmission	of	Cytomega	lovirus	Infection
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Modes of transmission	Risk of transmission (%)	Comments
Oral	60-80	common in child care centres
Respiratory	60-80	
Sexual (evidence: sudden increase in incidence at puberty and by DNA fingerprinting of cytomegalovirus isolates from partners)	25-50	
Breast feeding	40-60	
Blood transfusion	15	
In utero Primary infection 2nd trimester	40 0.2-0.7	mechanism of in utero, transmission not known; may be transmitted by white cells that ingested the virus

Clinical Manifestations

The most common signs and symptoms of congenital cytomegalovirus infection involve enlargement of the liver and spleen, liver dysfunction, petechiae, microcephaly, intracranial calcification, choreoretinitis, prematurity, and low birthweight. Cytomegalovirus pneumonitis will develop in 2% to 5%. Of those with congenital infections, about 5% have typical disease symptoms and signs, about 5% have atypical disease, and about 90% are asymptomatic and infection will not be recognized until developmental problems emerge. The mortality rate for infants symptomatic at birth is 30%, within the neonatal period.

No short- or long-term illness is known to result from intra-partum or post-partum (breast milk) infections.

Cytomegalovirus infections in organ transplant recipients who have received infected organs are often symptomatic (13% to 55%), but the severity of disease varies. Immunosuppression in these patients probably allows the disease to develop. Similarly, cytomegalovirus in patients with AIDS is common and can spread to the central nervous system and eyes.

Links to Infertility

Adverse Pregnancy Outcome

The overall prevalence of primary infection is 0.7% to 4% per gestation in seronegative women (higher in low-income groups). The rates of shedding range from 3% to 18% in the cervix (1.5% in first trimester to 13.5% at term); 3% to 9% in the urine; 1% to 2% in the pharynx; and 30% in breast milk during the first year after delivery. Like herpes simplex infections, congenital infection of the neonate is more common (43%) in seronegative women who develop primary CMV infection during pregnancy than in women with recurrent infections (3.4%) (Gilbert 1985).

Congenital Infections

In the United States, 4% to 20% of all infants become perinatally infected (Alford et al. 1990). Of these, about 80% to 90% of symptomatic infants and 8% to 15% of asymptomatic infants will develop sequelae. The most important sequelae for congenital cytomegalovirus infections are: progressive hearing loss, learning disability, neuromuscular problems, mental retardation, blindness, seizures, defect in the tooth enamel, and increased susceptibility to bacterial infections.

Animal Models

By infecting genetically different populations of mice either *in utero* or eight days after pregnancy, Fitzgerald and Shellam (1991) showed that host genetic factors can modulate the outcome of maternal and fetal infections. Severity of growth retardation, viability of fetus, and birthweight were significantly different for the three populations, though they were infected in a similar manner. The possibility of host genetic factors in humans may determine the outcome of infection as well.

Diagnosis

Culture and serology are the two methods of laboratory diagnosis for cytomegalovirus infections, as shown in Table 12.

Method	Specimen	Sensitivity (%)	Specificity (%)	Cost (\$)	Comment
Culture	urine, saliva	60-80	90-100	20	gold standard
Serology	blood	70-80	60-80	10	presence of IgM antibodies in neonates, diagnosis of congenital infections

Interventions

Treatment

No effective treatment or vaccine has been developed for congenital infection. An anti-viral drug, ganciclovir, is undergoing field trials. Its safety for use and efficacy in pregnancy need further study.

Prevention.

The high incidence and clinical severity of congenital cytomegalovirus infections following primary infection of women during pregnancy are of concern. Seronegative women of childbearing age should be counselled on the risk of development of CMV during pregnancy. If diagnosed, a woman with a primary cytomegalovirus infection during pregnancy should be counselled regarding poor fetal outcome.

Vaccine and Research Priorities

Live attenuated vaccine is now in experimental trial. Development of a subunit vaccine using the vital envelope glycoprotein appears promising. It can be efficacious without risk of latency and reactivation, a drawback of live attenuated vaccines. Little is known about latency except that the virus remains dormant in multiple sites in the body. cytomegalovirus is thought to suppress immunity in the host, its relationship to the host immune system remains unclear.

Human Papillomaviruses 9.

Introduction

Human papillomaviruses have been recognized as the etiologic agent of warts (papillomas) since early this century. Little is known about the biology of this virus as it cannot be replicated in cell culture. With advances in technologies in genetic research, the viral genome has been cloned from infected tissues and typed according to differences in DNA sequences.

Epidemiology

To date, more than 70 types are recognized, most of which are from genital sites and are likely sexually transmitted (Oriel 1990). Some genital isolates and mucosal or cutaneous warts (skin warts) may be the cause of respiratory papillomatosis in children infected at birth. Some types appear to be more frequently associated with transformation of epithelial cells to neoplasm. HPV-16 and HPV-18 are found in most squamous cell cancers of the lower genital tract, whereas HPV-6 and HPV-11, found in both respiratory and genital warts, are rarely associated with malignancy (ibid.).

Transmission

Papillomavirus infections are transmitted through skin abrasion (cutaneous HPVs), by sexual contact (genital HPVs), and by passage through the birth canal of an infected mother.

Studies in the United States have shown that approximately 12% of women attending STD clinics and 2% of women in student health clinics have evidence of HPV infection (Kiviat et al. 1989; Martinez et al. 1988). Studies by Kennedy et al. (1988) and Campion et al. (1988) have shown that over 40% of male partners of women with colposcopy-confirmed diagnosis of HPV infection had genital lesions or evidence of HPV in penile scrapings. These data suggest that male partners are an important reservoir of HPV infection.

Clinical Manifestations

The incubation period is 30 to 180 days. HPV probably gains entry to the epithelium through an abrasion in the skin. The virus enters dividing cells and multiplies. The infection appears to stimulate cell growth leading to the appearance of abnormal cells called "koilocytes." Replication of the virus is dependent on some aspect of host cell differentiation not yet defined; thus, the virus cannot be grown in culture.

HPV are implicated in cancer of various types in humans: cervical cancer is the most important of these. Penile cancer and anal cancer are also associated with HPV infection. A long latent period and a need for cofactors for the progression of papillomas to cancers suggest a multi-stage mechanism of carcinogenesis. Non-structural proteins from the virus have been found in pre-invasive as well as invasive cancers. The role of these proteins in the transforming process is not known, but results of experiments with different types of human cells suggest that host cells generally maintain control over virus replication and that mutations in the host cell may allow the transformation process to develop fully. Human and animal studies have shown that sunlight, diet, or radiation therapy may be the co-factors in various malignancies. HIV infection is associated with more rapid progression of HPV infection and with increased occurrence of cervical neoplasm.

Links to Infertility

The only apparent links to suboptimal pregnancy outcome may be in the rare transmission from an infected mother to her newborn, thus causing juvenile-onset respiratory papillomatosis. Juvenile-onset respiratory papillomatosis may manifest as early as 6 months or as late as 10 years after acquisition of HPV-6 or HPV-11 at birth.

Diagnosis

Clinical Diagnosis

Women with abnormal cytology on a cell smear are usually examined by colposcopy; however, the correlation between the two methods is about 60%.

Laboratory Diagnosis

Detection of viral DNA in lesion material by DNA probes is sensitive, especially if amplified by the polymerase chain reaction. The development of monoclonal and polyclonal antibodies to viral proteins may offer an alternative diagnosis based on antigen detection in the future.

The question still debated is the diagnosis or prognostic value of identification and typing of HPV, since the natural history of the disease is not known.

Interventions

Treatment

The traditional treatment for genital warts is podophyllin. Cryotherapy, carbon dioxide laser therapy, and interferon have been used with various degrees of success.

Prevention

For sexually transmitted HPV, prevention and control strategies should be targeted at education and prevention of acquisition at a young age to avoid this lifelong and potentially life-threatening infection.

Vaccine and Research Priorities

Vaccine work is difficult since there is no suitable animal model for the infection, and protective immunity is uncertain. Warts increase in number when the host is immunosuppressed (e.g., during pregnancy or after organ transplantation). Recurrence of genital warts is common, but it is not known how often this is due to reactivation of latent infection or a new infection with the same or different virus type.

10. Group B Streptococci

Introduction

Group B streptococci or *Streptococcus agalactiae* were initially recognized as pathogens of cattle-causing mastitis. In the last two decades, they have been recognized as the most important cause of perinatally transmitted infection to neonates in industrialized countries. Group B streptococci are classified into several serotypes on the basis of their immunological characteristics.

Epidemiology

Many women carry Group B streptococci in the vagina and cervix; the prevalence ranges from 4% to 29% (Baker 1980). The role of sexual intercourse in the spread of Group B streptococci is still controversial. Colonization in virgins is usually less than 5%, whereas sexually experienced women have a colonization rate of over 20%. This increases to as high as 35% to 40% in women with other STDs. At present, the general consensus is that Group B streptococci can be spread through heterosexual

intercourse but are likely also spread through the gastrointestinal tract and perhaps by other routes. Further studies are needed to determine their exact epidemiology.

Clinical Manifestations

Group B streptococci rarely cause disease in the vagina or cervix. Occasionally, urinary infections can be due to the organisms. Post-partum endometrial infections, premature delivery, and premature membrane rupture are rarely associated with Group B streptococci. However, they are usually non-invasive, non-pathogenic organisms in the female genital tract.

Infants born through the genital tract are at increased risk of acquiring Group B streptococci (Anthony et al. 1979). Estimates range from 2% to as high as 8% for the attack rate in infants who colonize extensively with Group B streptococci during vaginal delivery. Usually, infection becomes apparent within the first 72 hours of life. Pneumonia, sepsis, meningitis, and bone infection all occur during the neonatal period.

Links to Infertility

Currently, no links to infertility have been revealed for Group B streptococci.

Diagnosis

Group B streptococci grow well on blood agar media and produce readily recognizable colonies after 24 hours of incubation. The cost of a positive culture with biochemical confirmation and anti-microbial susceptibility profile is \$10 to \$12. A rapid and less expensive latex agglutination test is now commercially available.

Interventions

Treatment

Penicillin is effective against Group B streptococci. One of the penicillins is frequently the treatment of choice.

Prevention

Programs for identifying and treating Group B streptococci in colonized mothers have been studied quite extensively. The studies have identified women who are carrying Group B streptococci in their vagina and treating them during pregnancy, treating women during labour with antibiotics to prevent transmission of the infection to infants, and treating infants at birth. None of these approaches is being used routinely in Canada. Further operational research is needed to determine which strategies will be cost-effective and useful in the prevention of Group B streptococci in the newborn.

Research Priorities

Some of the issues to be resolved include:

- epidemiologic studies to determine the exact contribution of sexual intercourse to the transmission of Group B streptococci and to increase understanding of how the organisms disseminate;
- 2. strategies to immunize mothers to ensure that their infants will have antibodies to protect them from invasive infection; and
- 3. further studies of intervention with antibiotics before delivery, at delivery, or to infants colonized with Group B streptococci to determine which approaches can be introduced into routine obstetrical practice.

11. Hepatitis B Virus

Epidemiology

Hepatitis B virus is endemic in developing countries. The overall incidence in Canada has increased from approximately 4 per 100 000 population in 1987 to 11 per 100 000 population in 1990. Hepatitis B virus can be found in the blood, saliva, mucosal secretions, and semen of infected people. The four routes of transmission are:

- 1. parenteral: major source of infection, as blood contains large amounts of the virus;
- 2. sexual: heterosexual and homosexual transmission, especially with anal intercourse;
- 3. perinatal: transmission from mother to infant; and
- 4. "horizontal": spread within families.

In the United States, it is estimated that 25% of cases of the disease are sexually transmitted (Alter and Margolis 1990).

Clinical Manifestations

Hepatitis B virus enters the bloodstream from the mucosal surfaces of an infected person six days to two months after exposure and replicates within the liver cells. It also replicates in blood cells or bone marrow cells. Its restricted host range is presumably due to the presence of virus receptors on these cells. Most infections are self-limiting; over 95% of normal infected adults are able to clear the virus through their immune response. Those who cannot, such as immunocompromised individuals, become chronic carriers. They are asymptomatic and have high levels of hepatitis B virus persisting in their blood for years. Most infected neonates become chronic carriers.

The mechanism of liver damage in acute or chronic disease is not known. Host immune response by cytotoxic T cells may be involved in the

expression of disease. The ability of the virus to transform liver cells is associated with the development of cancer of the liver in chronic carriers.

Antibodies to the surface antigen of hepatitis B virus appear to be protective. The presence of antibodies to other parts of the virus can be found in the large amounts of virus in the blood. The role of these antibodies in protective immunity against hepatitis B virus is not known.

Links to Infertility

There is no evidence to associate hepatitis B virus with tubal factor infertility. However, it is implicated in adverse pregnancy outcome; infants born to infected mothers become chronic carriers of hepatitis B virus disease and have a risk of transmitting the disease and of developing cancer of the liver.

Diagnosis

Serum antibodies to different antigens of hepatitis B virus are detectable in commercially available immunoassays. Mass screening costs \$2 to \$3 per test.

Interventions

Treatment and Vaccine

Hepatitis B virus is the only sexually transmitted pathogen for which a vaccine is available. Protective antibody levels lasting seven years or more can be attained in 90% of adults who receive the vaccine. Protection is known to persist even after the loss of detectable antibody.

For people exposed to hepatitis B virus, either the vaccine, hepatitis B immunoglobulin, or both, injected intramuscularly will confer protection against becoming infected. The efficacy of the vaccine is 90% to 95% for infants born to mothers positive for hepatitis B virus surface or core antigen. The efficacy of the vaccine also depends on the time lapse between exposure to prophylaxis. The cost of the vaccine is substantial, and universal immunization is expensive. Recombinant DNA technology will likely decrease the cost of vaccine.

Prevention

In 1989, the National Advisory Committee on Immunization recommended universal screening of all pregnant women for hepatitis B virus, but implementation has not been uniform. People at increased risk of acquiring hepatitis B virus, such as health care personnel, children of carrier mothers, homosexually active men, and heterosexuals with multiple sexual partners or repeated STDs, should be immunized. Universal immunization will become an effective control strategy for hepatitis B virus when the cost of the vaccine decreases,

12. Human Sexually Transmitted Retroviruses

Introduction

The sexually transmitted retroviruses were discovered during the 1980s. Presumably, the number of retroviruses transmitted through intimate sexual contact will continue to increase. At present, human T-cell leukemia virus (HTLV-1) and the human immunodeficiency viruses (HIV-1 and HIV-2) are all known to be transmitted sexually.

These viruses share common features. They are all ribonucleic acid (RNA) viruses. In addition to some of their structural proteins, they all have similar envelope structures. A very specific enzyme called reverse transcriptase makes viral DNA from the RNA genome after entry into the host cell. Entry is gained into the host cell through attachment to a receptor protein called CD4, which is on the surface of specific lymphocytes called helper cells.

Once these viruses gain access to the cell, either they may proliferate and interfere with cell function and ultimately destroy the cell, or they may integrate their DNA into the host cell chromosome and become permanently inscribed into the host cell. Once a person is infected with any of the retroviruses, the infection is to be lifelong.

Epidemiology

Retroviruses are spread through sexual intercourse, through blood and blood products, including injections, and through mother to infant transmission.

Our knowledge about sexual transmission remains fragmentary. The female genital tract is not very susceptible to HIV-1; women having regular unprotected sex with an infected male partner have a risk of acquiring infection that is less than 5% a year in Western societies (Holmberg and Curran 1990). Anal intercourse increases the rate substantially as do concurrent infections with other STDs, particularly those that cause ulceration to the genital mucosa. Men are less susceptible than women to infection. In Western countries, the risk of a man acquiring HIV-1 from regular unprotected intercourse with an infected woman is probably less than 1% per year. The penis seems to be an unlikely point of entry for the HIV-1 virus. However, studies in Africa have suggested that the foreskin may be the major route for transmission, and most studies now support this observation (Plummer et al. 1991).

As a result of the varying heterosexual epidemiology of HIV-1, patterns of transmission have differed widely around the world. In countries where most men are not circumcised and where men frequently purchase sex from prostitutes, explosive heterosexual epidemics are occurring; in some countries over 20% of sexually active men are now infected (Quinn 1990). In these societies other STDs are often common and, as a result, sexual partners of infected men, particularly prostitutes, often have ulcers or

Illustrative Case — The HIV Iceberg

Janice is a 31-year-old assistant vice-president in a major corporation. She brings her seven-month-old son to a consultant paediatrician. After a normal pregnancy and delivery, her infant has had recurring episodes of respiratory infections, diarrhoea, and intermittent febrile illnesses. He also has a progressive pulmonary infiltrate on X-ray.

Janice has been monogamous with her husband for the past seven years. Before then she had three sexual partners, each for between 6 and 12 months sequentially. One of her sexual partners was a fellow graduate student whose home was in a country in which HIV is predominantly a heterosexual disease. Initially, with each new sexual partner, Janice insisted a condom be used. However, with all three partners once a stable relationship had ensued, she had agreed to continuing sexual relations without condom usage.

Janice has had no significant illness during the past six years other than a couple of prolonged episodes of vulval candidiasis.

Comprehensive evaluation of the infant disclosed a positive HIV test. Janice was also found to be HIV-positive; her husband is HIV-negative. It was possible to trace two of the three college sexual partners. Both of them were HIV-negative. The third partner has returned to his country of origin and could not be traced.

Learning Points

- HIV is an insidious disease that has to be considered with a wide variety of illness presentations in both adults and infants.
- Heterosexual spread is increasing rapidly in some societies. Due to its relative infrequence as a route of transmission in Canada, people continue to take risks with unprotected sexual intercourse with otherwise healthy people who could be infected with HIV.
- Education and information alone are insufficient to convince most people to take fewer risks.
- Although Janice has had several hundred coital episodes with her husband since the relationship began, he is not HIV infected. This illustrates the relatively low risk of female to male transmission.

cervicitis. These underlying STDs in women markedly increase the risk of HIV transmission from an infected man to a female sexual partner. In the United States, where HIV infection was spread primarily among homosexual men and injection drug users, the number of AIDS cases acquired through heterosexual transmission has increased 12-fold, from 250 in 1985 to about 3 100 in 1990. Of the 30 000 people who are estimated to be infected in Canada through 1991, probably less than 10% have been infected heterosexually. However, heterosexual spread is increasing in most industrialized countries, including Canada. The proportion of women presenting to the Ottawa Regional HIV Clinic with HIV infection increased from 2% in 1986 to 13% in 1991 (Fyke et al. 1992). Of the 63 women with

HIV infection treated at the clinic in 1991, 71% were sexually active, and, of these, only 27% used barrier STD prophylaxis. As long as women at increased risk because of behavioural factors become infected, or they become infected because of "seepage" of virus from groups at increased behavioural risk, heterosexual transmission of HIV will continue to increase in developed countries. At this time, women who have sex with bisexual men, with men from countries in which heterosexual HIV spread has occurred widely, and with men who use intravenous drugs are at increased

HIV-2 is largely restricted to West Africa and the former Portuguese areas of Africa. Its spread appears to be similar to that of HIV-1 and involves the same risk factors. It is not a problem in Canada at present.

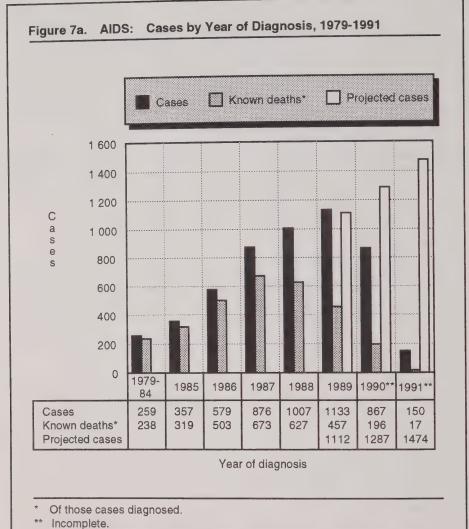
The epidemiology of HTLV-1 is not understood. It appears to be transmitted primarily by sexual intercourse. Its major focus continues to be the Caribbean and restricted areas in Africa and Japan.

Links to Infertility

None of the retroviruses is known to prevent conception directly. However, all of the retroviruses, in particular HIV-1, will have a major impact on fertility through loss of pregnancies and through illness and death of young, previously healthy, sexually active women. Their impact will likely be substantial in many parts of the world. In Canada, due to the limited spread of HIV-1 to women, its current impact is small. HIV-2 and HTLV-1 are not spreading in Canada, and they have little impact on the health of women.

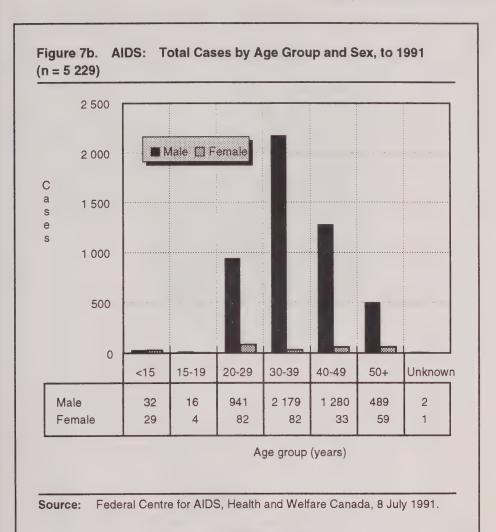
HIV-1 infects the fetus. Spontaneous abortions are occurring with increased frequency in areas of the world in which a significant proportion of women are infected with this virus. Also, prematurity and stillbirth are probably more common in women infected with HIV-1. The exact contribution of this virus to these three outcomes of pregnancy is still unknown. However, the evidence suggests that perhaps as many as one-third of pregnancies will be aborted, stillborn, or premature if the mother is infected with HIV-1. Much more information is required before the impact of HIV-1 on pregnancy is known.

Live-born infants of mothers infected with HIV-1 are at increased risk of being infected with this pathogen. At present, between 20% and 50% of infants born to infected mothers appear to be infected with HIV-1. It is unknown what proportion of infection occurs before delivery, during delivery, or post-natally. Ongoing studies in several countries should delineate the occurrence of infection in infants over the next one to two years. However, there are major concerns that breast milk can be a source of infection to infants. In Canada, women who are HIV-infected are encouraged not to breast feed their infants, but this obviously does not apply in developing countries, where the most infected women live.

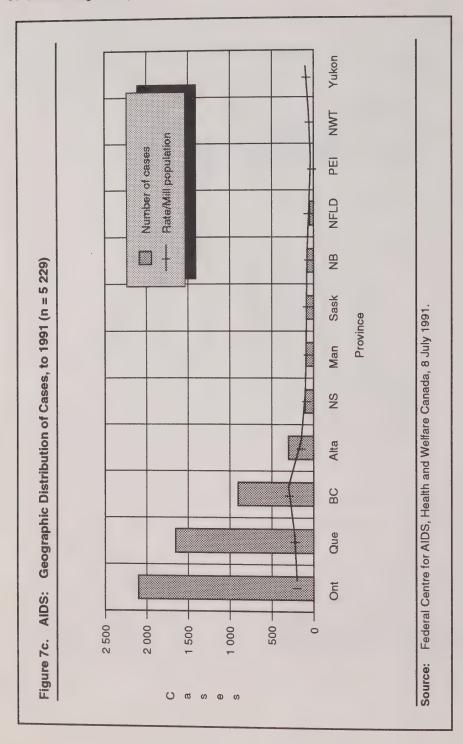


Source: Federal Centre for AIDS, Health and Welfare Canada, 8 July 1991.

Infected infants acquire a variety of other infections in a pattern similar to HIV disease in adults. About 17% to 39% of infected infants die before 12 months of age; another one-third die between their first and sixth birthdays (Scott et al. 1989; Blanche et al. 1990). The remainder will probably die of the complications of HIV disease within 10 years of acquiring the infection.



In Canada, about 200 HIV-infected mothers gave birth in 1991; if onethird of the infants were infected, about 70 infants will have been born with HIV infection. The situation requires continuing major efforts to slow the spread of HIV transmission, particularly heterosexual transmission. We can be reasonably satisfied with many of the control initiatives taken to impede the rapid dissemination of HIV infection into the population.

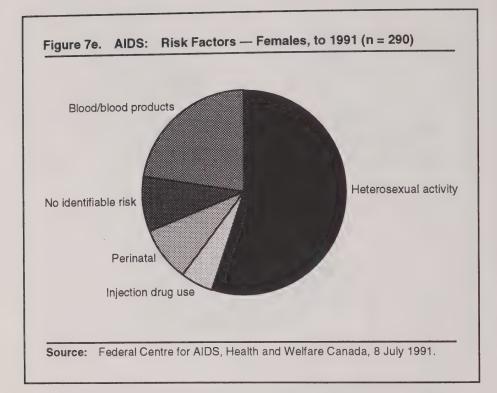


AIDS: Risk Factors — Males, to 1991 (n = 4 939) Figure 7d. Injection drug use (IDU) Perinatal Homosexual/bisexual and IDU Blood/blood products Heterosexual activity No identifiable risk Homosexual/bisexual activity Federal Centre for AIDS, Health and Welfare Canada, 8 July 1991. Source:

Diagnosis

Clinical Diagnosis

Within three months of acquiring infection, a subset of individuals (10% to 50%) experiences an illness that resembles infectious mononucleosis. Recovery from this illness is usually complete, and the individual remains well for the next 3 to 20 years. This interval is referred to as the "latent period." At some point, viral multiplication occurs, and the infected patient presents with swollen glands, weight loss, night sweats, chronic diarrhoea, or increasing fatigue. As the infection progresses, the immune system breaks down. Opportunistic bacterial, viral, and fungal infections, which are usually self-limiting in an immunocompetent person, disseminate in the skin, mucous membranes, gastrointestinal tract, kidney, brain, and lungs of a person infected with HIV.



(a) Detection of HIV by Culture

This method requires co-cultivation of the patient's white blood cells with normal white blood cells. Depending on the amount of virus present in the sample, culture may take weeks to become positive. It requires technical expertise and stringent containment facilities, which make it very expensive.

(b) Detection of Antibodies to HIV by Serology

The enzyme immunoassay (EIA) is used to give a presumptive laboratory diagnosis of HIV infection. It is the least expensive technique, is technically easy to perform, and is amenable to batching large numbers of specimens. Positive or indeterminate EIA results are usually confirmed by reacting the patient's serum with HIV proteins impregnated on strips of nitrocellulose paper (immunoblot). Although the performance characteristics of these serologic tests approach those of culture and results can be obtained in four hours, the disadvantage of serology is that there is a "window period" before antibodies to HIV are detectable in an infected individual.

The "window period" is variable, ranging from three weeks to three months, with 98% of seroconversions occurring within six months. The

"window period" can be more prolonged in a small subset of individuals who fail to produce antibodies to HIV despite being culture-positive.

Detection by Gene Probe (c)

The development of gene probes based on amplification of viral DNA by polymerase chain reaction technology has facilitated the detection of a single virus in a blood sample. The test can be completed within six hours of receipt of the specimen. This test requires stringent quality control because of its sensitivity to ensure that there is no cross-over contamination from other specimens. At present, polymerase chain reaction detection is limited to research laboratories and tertiary care facilities.

Table 13. Laboratory Diagnosis of Human Immunodeficiency Virus Infections

Method	Specimen	Sensitivity (%)	Specificity (%)	Cost (\$)
Culture	white blood cells*	90-100	98-100	20-25
Serology Elisa	hds a d	00	00	0.40
Immunoblot	blood	99	99	8-10
Gene probe	blood	99	99	15

The frequency of HIV isolation from infected people varies according to body site. The range is 14% to 17% from tears and bone marrow, 40% from saliva, and over 50% from genital secretions, cerebral spinal fluid. and the brain (Carlson and Jennings 1990).

Interventions

Treatment

A variety of agents are being studied for use in both adults and infants for the suppression of HIV virus. At present, zidovidine (AZT) is the usual treatment modality, and it has limited efficacy. Current evidence suggests it prolongs life by one to two years after an AIDS-defining illness in adults.

Studies in children are less conclusive.

Vaccine

Much effort has been directed toward the production of a vaccine that elicits neutralizing antibodies against the virus. The search for an effective vaccine has been frustrated by the lack of a suitable animal model and by the frequent mutations of the viral envelope protein. A vaccine to block the virus from attaching to the host cell is also being sought. Passive immunization, which is successful for hepatitis B virus, did not prevent HIV

in chimpanzees. The pathogenesis of HIV infection needs to be better understood before an effective vaccine can be developed.

Prevention

The only effective strategy to reduce the impact of HIV on society is

through well-designed prevention initiatives.

Widespread efforts to educate sexually active youth and adults have occurred in most settings through mass media and other initiatives. The efficacy of such educational initiatives in changing behaviour is under review.

Other strategies used for STDs have not yet been used widely for the control of HIV. These include contact tracing and screening of men and women with high-risk behaviour, including those with STDs. Intensive counselling of men and women with high-risk behaviour either in groups or individually needs to be considered as a preventive strategy.

Part 3. Sequelae of Sexually Transmitted Diseases

Pelvic Inflammatory Disease

Definition

PID is an infection of the upper reproductive tract of women. It can include infection of the endometrium (endometritis), fallopian tubes (salpingitis), or ovaries (oophoritis). Commonly, infection spreads into the pelvic tissues to cause a pelvic peritonitis. Occasionally, infection spreads to involve contiguous structures, including the bladder, the intestines, or liver, and produces inflammation, adhesions, and occasionally malfunction of these organs.

The common sequelae of PID include infertility, ectopic pregnancy, and chronic pelvic pain with dyspareunia (painful intercourse).

Epidemiology

About 10% of women have had an episode of PID; about 100 000 new cases probably occur in Canada each year. The highest annual incidence occurs among adolescents, with the risk being estimated to be over five times as great for a sexually active 12- to 15-year-old compared to a 20- to 24-year-old (Shafer and Sweet 1989). If current trends continue, almost 50% of women who were 15 years of age in 1970 will have experienced at least one episode of PID by the year 2000 (ibid.), and one in four women in the United States will have PID by the year 2000.

The trends over time in Canada for hospital admission for PID are summarized in Figures 8a and 8b. No comparable data exist for non-hospitalized outpatient PID cases in Canada. However, an increasing proportion of PID cases are cared for outside hospital; thus, Figures 8a

and 8b significantly underestimate total cases. In the United States, 65% to 80% of PID cases are treated outside hospital.

The proven risk factors for the increasing risk of PID include lower socioeconomic status, lower levels of education, younger age at first intercourse, multiple sexual partners, vaginal douching, the use of an IUD, and concomitant HIV infection (Cates et al. 1990).

The financial costs of PID are substantial. The direct cost to the Canadian health care system for the management of acute illness in 1991 probably approached \$200 million. The average hospital stay was 6.2 days, and 40% of patients had surgery (Todd et al. 1988). The direct cost of long-term sequelae is probably at least \$100 million. These figures have been extrapolated from the costs of PID in the United States and are an estimate from earlier Canadian figures. Also, they do not include the economic cost of loss of work, the indirect cost of lost productivity, and the psychosocial cost.

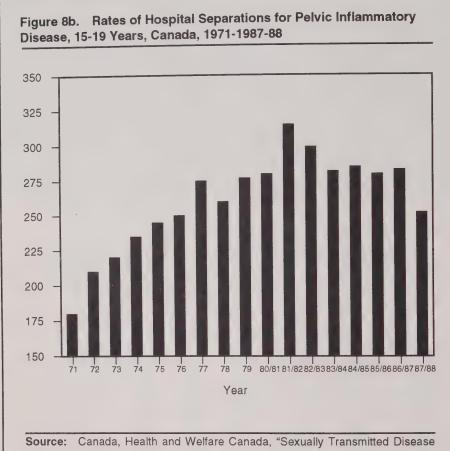
Figure 8a. Age-Specific Rates* of Hospital Separations for Pelvic Inflammatory Disease, Canada, 1971-1984

	Age group (years)						
Year	15-19	20-24	25-29	30-34	35-39	40-44	Total
1971	185.9	318.9	309.9	300.7	246.8	158.9	254.1
1972	202.9	328.8	323.8	295.9	242.8	153.8	259.8
1973	218.0	352.2	318.7	290.0	220.2	157.4	266.1
1974	232.2	351.4	321.1	284.2	233.7	146.2	269.6
1975	241.3	348.1	330.7	273.8	210.0	131.9	268.3
1976	245.6	380.3	329.5	292.0	212.2	137.7	276.8
1977	270.1	403.7	356.5	300.8	217.1	141.9	296.4
1978	259.7	401.1	357.0	283.9	221.2	137.5	291.4
1979	271.8	405.0	363.6	281.5	189.6	. 124.7	291.0
1980/81	281.0	432.0	374.1	295.3	195.3	128.3	301.6
1981/82	308.0	435.5	377.6	292.2	196.0	125.0	307.0
1982/83	294.3	425.1	375.4	283.2	196.5	120.2	299.2
1983/84	275.7	404.7	381.5	279.1	188.5	116.2	289.6
1984/85**	286.6	403.3	370.6	285.3	191.5	113.0	289.1

^{*} Per 100 000 population.

Source: Canada, Health and Welfare Canada, "Sexually Transmitted Disease in Canada 1987," Canada Diseases Weekly Report 15 (Suppl. S2) (April 1989), 14.

^{**} The last year for which data are available from Statistics Canada. Since 1980 all hospital morbidity data have been reported by fiscal year.



Source: Canada, Health and Welfare Canada, "Sexually Transmitted Disease in Canada 1987 [Updated to 1987-88]," Canada Diseases Weekly Report 15 (Suppl. S2) (April 1989), 14.

In the industrialized world, PID is responsible for about 25% of infertility, and at least 50% of ectopic pregnancies are considered to be due to the sequelae of previous episodes of PID (Weström 1980a).

Etiology and Mechanisms of Disease

Two sexually transmitted pathogens, *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, are responsible for about 80% of cases of PID. These organisms initially infect the cervix and may cause either symptomatic or undetected disease at this site. Upper tract invasion commonly occurs with menses, and two-thirds of symptomatic episodes of PID occur within one week of the onset of menses. Both *N. gonorrhoeae*

and C. trachomatis ascend through the cervix into the endometrial cavity and into the fallopian tubes. There, they cause injury to normal cell function, produce acute inflammation with migration of neutrophils (pus cells) into the wall of the tubes, and lead to chronic inflammation, fibrosis, scarring, and occlusion.

N. gonorrhoeae and C. trachomatis work in synergy so that infection with the two seems to be more rapidly invasive and causes more acute and chronic damage to the fallopian tubes. In addition, the two pathogens appear to break down normal host defences and permit other organisms, such as bacteroids, Haemophilus influenzae, anaerobic streptococci, and mycoplasma, which are part of the normal vaginal flora, to ascend through the cervix into the upper tract and cause disease. As a result, at the time of surgery for acute PID with drainage of pus, several organisms often are found in the pus that are normally resident in the vagina and not known to be sexually transmitted. Such organisms alone are much less frequent causes of invasive disease.

In about 20% of patients who have PID, no sexually transmitted pathogen can be identified. This occurs more commonly in patients with an IUD. Presumably, a varying proportion of PID is associated with a breakdown of host defences against normal flora ascending from the vagina and creating disease in the upper genital tract, and is not due to sexually transmitted infections. However, further studies are needed to determine if other potentially invasive, injurious micro-organisms, perhaps currently unknown, can be sexually transmitted and cause PID in some women.

Adolescent PID

Figure 8b shows a dramatic increase in the rates of hospital separations for PID in the 15- to 19-year age group in Canada from 1971 to 1988.

The incidence of STDs in an adolescent prenatal clinic in Winnipeg, Manitoba (Table 14), illustrates the potential for developing sequelae of sexually transmitted infections in this population (Morris 1990). These individuals will likely experience the damaging consequences of their sexually transmitted infections when they want to be pregnant. Silent STDs, such as chlamydial infections and silent PID, are compelling reasons for allocation of resources for targeted screening programs in this population.

Diagnosis

A lack of standardized criteria makes the diagnosis of PID difficult, expensive, and imprecise. At present, most physicians make the diagnosis on the basis of a characteristic syndrome consisting of lower abdominal pain, pain on cervical motion, and tenderness in the pelvis on deep vaginal examination, accompanied by fever. Abnormal bleeding, cervical inflammation, and vaginal discharge also are often present. Cultures are usually obtained only from the cervix. More invasive procedures are rarely done to aspirate pus from the tubes or to insert a laparoscope into the pelvis to see the upper tract and to take pus samples from specific sites.

Table 14. Incidence of STDs in Adolescent Prenatal Clinic, Winnipeg

	Ages ≥12 to ≤18		
	First visit (%)	36 weeks (%)	
Gonorrhea	8	1	
Chlamydia	26	9	
Trichomonas	11	12	
Herpes	2	2	
Condyloma	9	9	

Source: M. Morris, "Adolescents and STDs in Winnipeg," *Canadian Journal of Obstetrics and Gynaecology* 1 (October 1990), 95.

Silent or asymptomatic PID must be common. About one-half of women with infection leading to tubal infertility or ectopic pregnancy have no history of acute PID. At present, no test is available to diagnose asymptomatic PID before complications bring it to medical attention. As a result, physicians must have a high index of suspicion, and treat whenever this diagnosis is seriously considered.

Natural History

Without treatment, most patients recover clinically after an acute illness of 5 to 10 days. However, most women may remain at substantial risk of ongoing inflammatory damage in the pelvic area. A few patients develop large tubal or pelvic abscesses that require surgical drainage and sometimes can be cured only by having a hysterectomy.

After recovery, the possibility of a second episode of PID is increased tenfold. The rate of ectopic pregnancy is eight times greater among women with a history of PID than among those who have no history. Tubal infertility occurs in about 20% of patients who have had one episode of PID and in over 50% of patients who have had three episodes. In addition, chronic debilitating pelvic pain, which may prevent satisfactory sexual intercourse, occurs in 10% to 15% of women after having an episode of PID.

Among 50 women in Winnipeg who were followed up after an episode of PID, 23 subsequently wanted to become pregnant. Of the 10 who had had gonococcal PID, all became pregnant, compared to 6 of 13 who had had non-gonococcal PID. Of the 7 failures, 3 had had *C. trachomatis* infection and 4 had had a tubal abscess with PID (Brunham et al. 1988).

Treatment

Treatment regimens are controversial. Standard recommendations have included a drug to treat gonococcal infection and one to treat chlamvdia. No one drug has been proven to treat both pathogens predictably well.

Few treatment trials have ensured that a healthy, normally functioning, fertile genital tract was the identified outcome of treatment. Most studies have measured only a clinical response over the course of therapy and have not obtained long-term follow-up to evaluate fertility prognosis. Although standard regimens and treatment guidelines have been suggested by Health and Welfare Canada and by the U.S. Public Health Service, most have not been adequately investigated in large groups of patients. Much more needs to be known about optimal therapeutic approaches to acute PID. Also, it is not known if any anti-microbial treatment is useful for chronic PID.

Prevention

Priorities are required to reduce the impact of PID on women in Canada, including the long-term sequelae. They include:

- primary prevention programs to ensure that women do not become infected with N. gonorrhoeae or C. trachomatis:
- early recognition of these infections and immediate appropriate treatment to eradicate infection before it has ascended to the upper tracts; and
- more effective treatment programs to ensure satisfactory outcomes if infection has led to salpingitis and to prevent the long-term sequelae of tubal infection and ectopic pregnancy.

Research Priorities

Research into the management of PID and its sequelae is not well supported in Canada. Until recently, it has not been a priority, and little research funding has been provided for fundamental or applied studies. A review of the annual compilation of health research funded in Canada in 1990-91 indicated that only three investigators had received funds to conduct research into PID. Research priorities in this area should include:

- more definitive studies on the epidemiology of the disease;
- clinical studies on simple diagnostic parameters;
- studies to identify etiology, particularly in patients from whom N. gonorrhoeae and C. trachomatis cannot be isolated:
- studies of pathogenesis to understand how PID occurs;
- studies to diagnose tubal involvement in patients with PID;

Illustrative Case — Silent PID and Ectopic Pregnancy

Laurel is a 26-year-old geologist who is currently employed on a project in Tanzania assisting in an oil exploration program. Her husband Geoff works on the same project as a surveyor.

Laurel presents at a Mission Hospital with eight hours of severe pain in her lower abdomen. Her menses have been quite irregular. Although her last menses were seven weeks earlier, she was uncertain as to whether she was pregnant. She had not been examined by a physician until her acute presentation.

When examined in the Mission Hospital, she was hypotensive (BP 70/40) with tachycardia (160), and clinically she was in shock. After establishing intravenous lines, she was transfused with emergency blood and taken to the operating room. At laparotomy she had a peritoneal cavity full of blood and a ruptured left fallopian tube. The tube was excised and the bleeding controlled. The right tube was noted to be tortuous and dilated. She made an excellent recovery and returned to work 10 days later.

On return to Canada, Laurel requested studies be done to determine if she had ever had *C. trachomatis* infection. Also, she discussed her situation with a STD expert.

She did have antibodies to *C. trachomatis*. Both Laurel and Geoff have been monogamous since their relationship began five years earlier. Between 17 and 22 years of age, Laurel had four sexual partners. For most of this time she had taken oral contraceptives and she had not used any other precautions to prevent STDs. However, she had noted that her menses had become irregular and more painful at about age 20. Also, on several occasions she had consulted her gynaecologist about discomfort on intercourse. However, at no time did she have a recognized episode of acute PID and she had never been treated for a sexually transmitted infection.

Learning Points

- C. trachomatis is insidious; probably between 50% and 70% of sequelae, including ectopic pregnancy and tubal infertility, are not preceded by recognized symptomatic illness.
- Ectopic pregnancies are one of the most life-threatening complications of gestation, with a substantial mortality if medical assistance cannot be obtained quickly.
- *C. trachomatis* is frequently transmitted by men who have either no symptoms or so few symptoms they do not seek investigation.
- Strategies to control the spread of chlamydia are required.
- Strategies to screen asymptomatic men are important to control C. trachomatis.

- research on less invasive or non-invasive methods of assessing tubal function after a sexually transmitted infection or PID and for assessing efficacy of treatment regimens;
- studies of risk factors to determine if modification of such factors can decrease the recurrence of PID;
- studies to understand the links between PID and its sequelae ectopic pregnancy and tubal infertility;
- studies to identify the potential of immunization to prevent either infection with *N. gonorrhoeae* or *C. trachomatis* or upper tract invasion;
- community-based prevention studies, including educational and behavioural components in addition to traditional health system interventions; and
- studies of various treatment options including long-term followup of sequelae.

Ectopic Pregnancy

Definition

Ectopic pregnancy is defined as a pregnancy in which the fertilized egg is implanted on any tissue other than the endometrial cavity. This includes implantation in one of the fallopian tubes, the ovaries, the uterine cornua, or the abdominal cavity. It was first described in 963 AD in Arabic writings on surgery. Early treatments ranged from starvation to purgation to electrocution of the fetus. With improved diagnostic and treatment methods, the mortality in Canada is about 1%. Worldwide, mortality due to ectopic pregnancy accounts for 5% to 12% of all maternal deaths.

Epidemiology

The prevalence of ectopic pregnancy relates to the number of fertile women exposed to becoming pregnant and to the distribution of risk factors among that population (Chow et al. 1987).

The known risk factors are (1) increasingly older age, (2) post-infection tubal damage (e.g., post-PID), (3) post-surgical tubal damage (e.g., tubal ligation), (4) tubal pathology, (5) use of an IUD, and (6) douching. Embryonic and chromosomal anomalies may also predispose a woman to ectopic pregnancy.

Significant increases in the ratio of ectopic pregnancy to intrauterine pregnancies have been observed in almost all industrialized societies since the 1950s. The proposed reasons for the rise include increased use of tubal sterilization; increased use of IUDs; delay in conception for women; and the increased incidence of PID due to STDs.

In Canada, the incidence of ectopic pregnancy, as documented by hospital separation data, has increased from 5.7 ectopic pregnancies per

1 000 pregnancies in 1971 to 12.9 in 1984-85 (Hockin and Jessamine 1984); this represented 1 ectopic pregnancy in every 77 pregnancies. In 1987-88, 1 in every 62 pregnancies in Canada was ectopic (Figure 9a). Of interest is the ectopic pregnancy in younger age birth cohorts from 1939 to 1964 (Figure 9b), which is probably related to the increasing incidence of STDs in these cohorts and the other reasons described previously. A similar increase in ectopic pregnancies has been reported in the United States, where there was a fourfold increase in incidence from 4.5 to 15.2 ectopic pregnancies per 1 000 reported pregnancies from 1970 to 1985.

Etiology

Studies in Canada, the United States, Sweden, and Finland have shown that N. gonorrhoeae and C. trachomatis are the major causes of

acute PID and consequently ectopic pregnancy.

Brunham et al. (1986) correlated tubal pathology, *C. trachomatis* isolation, and antibody levels with ectopic pregnancy in 50 women. Based on a review of the literature, Kosseim and Brunham (1986) estimated that about 30% of ectopic pregnancies are due to prior *C. trachomatis* infection. In a study of 104 infertile women in Finland, antibodies to *N. gonorrhoeae*, *C. trachomatis*, and *M. hominis* were found in 14%, 40%, and 37%, respectively, in women with tubal factor infertility, compared to 0%, 7%, and 14% in infertile women with normal fallopian tubes (Miettinen et al. 1990). Among the women with tubal factor infertility, 20 had a history of ectopic pregnancy; of those, 8 (40%) tested positive for *C. trachomatis*, 7 (35%) for *M. hominis*, and 1 (5%) for *N. gonorrhoeae*.

Approximately half the women who had had ectopic pregnancies had histologic evidence of prior salpingitis. In an extensive study of infertility, in women 15 to 24 years of age, after one laparoscopically verified episode of PID, 12.6% were either infertile as a result of the infection or had had an

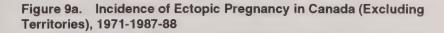
ectopic pregnancy.

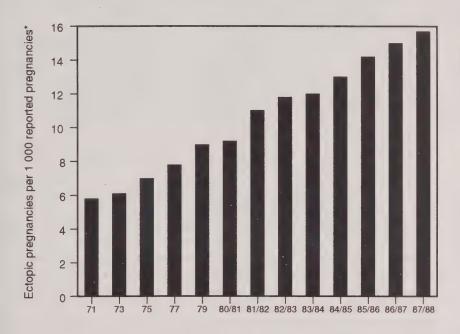
As many as 80% of women who have had an ectopic pregnancy have not had a history of symptomatic PID (Brunham et al. 1992). These women have sustained PID, and *C. trachomatis* is considered the major cause of silent or atypical PID.

Weström et al. (1981) calculated that the risk of ectopic pregnancy for women 20 to 29 years of age who had had one episode of PID was 2.0 compared to 0.3 for women with no previous history of PID. Women who have had a single episode of PID are therefore 7 to 10 times more likely to have an ectopic pregnancy as women who have not.

Pathogenesis

Like PID, the pathogenesis of tubal damage by sexually transmitted pathogens remains unclear. Three hypotheses have been proposed: (1) persistent low-grade infection of the fallopian tube inducing chronic inflammation; (2) post-infectious damage with permanent residual fibrosis or mucosal disruption; and (3) immunopathologic damage engendered by a cervical infection.





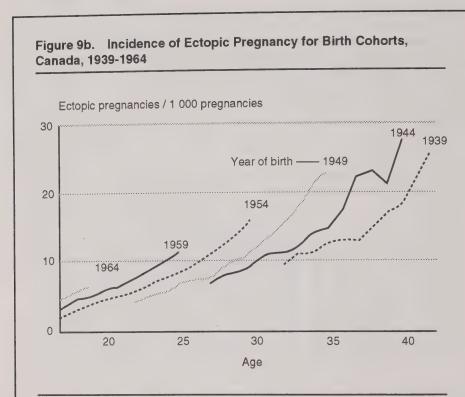
Live births, stillbirths, legal abortions, and ectopic pregnancies. Source: Canada, Health and Welfare Canada, "Sexually Transmitted Disease in Canada 1987 [Updated to 1987-88]," Canada Diseases Weekly Report 15 (Suppl. S2) (April 1989), 15.

Clinical Manifestations

The most common symptoms are abdominal or pelvic pain, vaginal bleeding due to uterine sloughing as a result of death of the embryo, and delay in menstruation. Less common symptoms are dizziness or fainting due to hypotension, nausea, breast engorgement, and passage of tissue. Abdominal and adnexal tenderness is usually present on examination. The patient may be hypotensive or in shock from intra-abdominal blood loss.

Diagnosis

The clinical diagnosis of ectopic pregnancy may be accurate only in 50% of cases. Diagnostic aids used to confirm or exclude ectopic pregnancy are (1) serum pregnancy tests using radioimmunoassay techniques



Source: Canada, Health and Welfare Canada, "Sexually Transmitted Disease in Canada 1987," *Canada Diseases Weekly Report* 15 (Suppl. S2) (April 1989), 15.

that provide high sensitivity and specificity (most ectopic pregnancy produces only low levels of human chorionic gonadotropin); (2) ultrasound, which is sensitive and specific in the diagnosis of an intrauterine pregnancy and therefore useful for the exclusion of an ectopic pregnancy; (3) culdocentesis, which identifies blood in the cul-de-sac of 80% of ectopic pregnancies; and (4) laparoscopy, which allows good visualization of pelvic structures that have no adhesions. Five percent false-positive rates have been reported using these procedures; however, the use of a combination of these procedures is satisfactory for diagnosis (Ory 1992).

Treatment

Surgical procedures such as salpingostomy or salpingectomy are usually successful treatment for ectopic pregnancy. In a retrospective study, Sherman et al. (1982) reported that subsequent to salpingostomy, patients with a history of abnormal fertility have a 76% intrauterine

pregnancy rate and a 5% repeat ectopic rate, compared to 44% and 9%, respectively, in patients who had radical surgery (salpingectomy).

The prognosis after ectopic pregnancy is thought to be: one-third (up to 50%) are infertile in some studies; one-third are able to proceed with a normal-term intrauterine pregnancy; and one-third experience pregnancy misfortune either as a repeat ectopic pregnancy or pregnancy miscarriage.

Intervention

Because of the need for hospitalization and surgery, the cost of ectopic pregnancy to the health care system is substantial. Since little is known about the events that precede an ectopic pregnancy, more research into its etiology and pathogenesis is needed before effective intervention strategies can be designed to prevent STDs and ectopic pregnancy.

Tubal Factor Infertility

Definition

Infertility has been defined as "the absence of recognized conception after one year of regular intercourse without the use of contraceptive." By this definition, the prevalence of infertility among couples desiring a pregnancy is about 20% in Canada. Collins et al. (1984) in Nova Scotia reported that tubal infertility was the cause for infertility in 17% of 1 297 couples. However, infertility is relative, and of 100 couples who meet this diagnostic criterion, about 50 become pregnant within 10 years.

Tubal factor infertility identifies conception failure caused by obstructed or malfunctioning fallopian tubes. This can be due to congenital causes, salpingitis, or previous pelvic surgery, including tubal ligation. This review will focus on salpingitis as a cause of tubal factor infertility.

Etiology

The relationship among STDs, PID, and tubal infertility is complex. The components of this relationship are depicted in Figure 10. At present, the only two pathogens proven to cause tubal factor infertility are N. gonorrhoeae and C. trachomatis. In Canada in 1991, the lifetime risk of a woman acquiring either of these pathogens depends on the risk factors already identified in Parts 1 and 2. The prevalence of N. gonorrhoeae has been decreasing, and most sexually active women likely now have a lifetime risk of acquiring N. gonorrhoeae of less than 5%. On the other hand, the incidence of C. trachomatis has continued to increase, and the lifetime risk of acquiring C. trachomatis is probably between 20% and 30%. The incidence of PID in women infected with N. gonorrhoeae, C. trachomatis, or both is unknown and also depends on other factors. However, in most studies it ranges between 30% and 50%. In particular, silent PID with the development of sequelae years later is common with C. trachomatis; in some studies over one-half of the patients who have tubal factor infertility or have had an ectopic pregnancy do not recall an episode of PID (Brunham

(Undiagnosed) (Diagnosed) Proposed Schema for Progression of Sexually Transmitted Diseases to Tubal Infertility Tubal infertility GE GE Ge Asymptomatic Symptomatic Š Cervicitis ð Figure 10.

Ct — C. trachomatis. Gc — N. gonorrhoeae.

et al. 1986; Sellors et al. 1988). As a result, the links between sexually transmitted infections and tubal factor infertility are not obvious to patients and care providers. However, studies from Sweden and Canada have clearly indicated that the temporal relationships and the causal inferences between these pathogens, PID, and tubal infertility are real. Over 30 studies now clearly identify this relationship (Cates and Wasserheit 1991).

The severity of pelvic inflammation as determined by laparoscopy relates to fertility outcome; severe disease is five times more likely to lead to infertility than mild disease.

Epidemiology

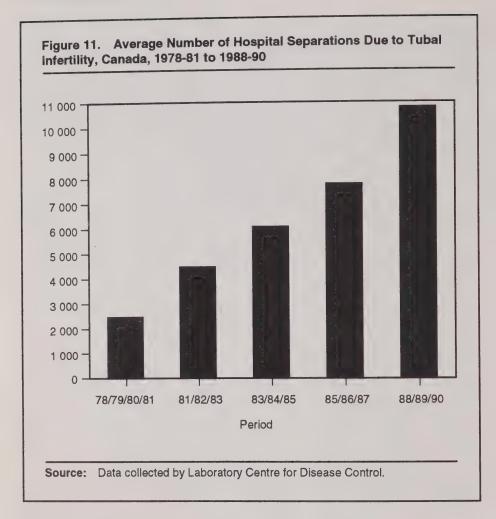
Tubal malfunction or obstruction is usually not apparent to a woman until she desires conception and fails to become pregnant. Although perhaps one-half of these women have had a history of PID or ongoing symptoms that suggest a chronic pelvic illness, most are asymptomatic.

As a result the epidemiology is difficult to ascertain precisely. Extensive investigation is also required to diagnose tubal infertility accurately. This diagnosis can only be determined by a specialist, and many women may not have access to this level of health care. Tubal infertility due to salpingitis is the most common reason for tubal reconstructive surgery and for in vitro fertilization.

The hospital separation data for infertility due to tubal congenital anomalies and tubal occlusion in Canada from 1978-1981 to 1988-1990 are shown in Figure 11. However, a different number of centres report the data every year. Thus, although an increase in the number of cases is apparent, the validity of the trend cannot be assessed.

In Canada and other industrialized countries, between 20% and 30% of female infertility is due to previous episodes of PID. In developing countries, some studies have shown the incidence of PID as the major contributing factor to female infertility to be 70% or more. In the United States, 125 000 new cases of infertility due to STDs are estimated to occur each year. Extrapolation in Canada would suggest that perhaps as many as 10 000 new cases occur annually. However, only about one-half of these infertile women may want additional children and therefore would be identified as having a reproductive problem when they sought medical care. In 1984-85, 2 047 women were hospitalized for tubal factor infertility investigation for an average of four days at an estimated cost per case of \$3 916, or a total cost of \$8 016 052 (Todd et al. 1988). It is estimated that between 60 000 and 70 000 Canadian women have tubal infertility due to a STD.

Some prospective studies have indicated about one-half of women infected with \hat{N} . gonorrhoeae and about one-quarter infected with C. trachomatis develop upper genital tract invasion with salpingitis and endometritis. Of these, about 15% to 20% develop tubal infertility after the first episode; about 60% are infertile due to tubal factors after three or more episodes of PID (Weström 1980b).



Risk Factors

The risk factors for tubal infertility, in addition to those associated with STDs and PID, include the following:

- it is less common in women taking an oral contraceptive;
- it is more common in older women after an episode of PID;
- specific antibiotic treatment does not seem to relate to the prevention of infertility;
- women with IUDs and PID seem to be at increased risk of tubal infection compared to those without IUDs; and
- smoking appears to increase the risk of tubal infertility; however, the relationship is uncertain and may be due to factors other than smoking itself.

Pathogenesis of Tubal Infertility

Longitudinal studies in women from Lund, Sweden, have provided the best evidence linking STDs to salpingitis and infertility. Only salpingitis due to N. gonorrhoeae or C. trachomatis has been proven to result in infertility. Gonococcal infection was first recognized during the 1930s as a cause of infertility. So far, the respective contribution of N. gonorrhoeae and C. trachomatis has never been delineated clearly. However, many investigators have shown that tubal obstruction or malfunction is associated strongly with the presence of chlamydial antibodies.

Current evidence suggests that N. gonorrhoeae produces a more invasive acute infection, which leads more frequently to health-seeking behaviour and treatment. Chlamydial infection is often mild and subacute. However, prolonged and untreated infection can cause as much damage as gonococcal infection and can lead to chronic inflammation, scarring, and tubal obstruction. The histopathology produced by C. trachomatis in the fallopian tubes is similar to that produced by the same organism in the conjunctiva, which causes chronic progressive scarring and ultimately blindness. Also, the results of several studies have revealed that C. trachomatis can persist for months and perhaps even years within the tubal mucosa, perhaps leading to progressive injury. Although we may fail to isolate the infectious organism using traditional culture technology, it can likely remain latent for long periods of time and produce continuing disease.

Diagnosis

Tubal infertility is likely to be present in women who present with a history of PID, adnexal masses, or other findings that suggest previous episodes of PID. However, a definitive diagnosis requires visualization of the tubes either by direct inspection through endoscopy (through the vagina or the anterior abdomen) or by injecting contrast material into the endometrial cavity. Although such procedures are expensive and invasive, they are necessary before any definitive diagnosis can be made or any operative treatment can be considered.

Treatment

Tubal reconstruction is commonly done to correct tubal infertility. Occasionally, adhesions can be removed and significant function can be restored, with subsequent conception. However, other procedures are often required for patients who have obstructed, dilated, and non-functioning tubes. Surgical procedures include "making a window" in the wall of the fallopian tube, resecting the obstructed area, re-attaching more normal tubal structures to the uterus, and removing pus or other inflammatory response to infectious agents. None of these procedures has a high success rate; subsequent pregnancy varies from a low of 10% in patients with severely damaged tubes to about 30% in women with less damage. Overall, the success rate of tubal surgery in most studies is about equal to or slightly better than that of IVF.

Prevention

If public health policies and educational initiatives are introduced to the general public and to health care providers and are successful in reducing the occurrence of *N. gonorrhoeae* and *C. trachomatis* in the population, the incidence of tubal infertility should decline in the next 10 years. These strategies have been identified previously.

Treatment strategies for PID may also reduce the occurrence of tubal infertility, but this is unproven. Continued concern about persisting *C. trachomatis* infection as an ongoing cause of further damage deserves additional study. At present, no evidence suggests that the organisms persist and cause the progressive destructive fibrosis associated with tubal infertility. However, more definitive studies using molecular technology have shown that *C. trachomatis* genetic material persists inside cells in the tubal epithelium. As a result, long courses of effective treatment for *C. trachomatis* should probably be evaluated in patients with PID as an experimental strategy to prevent tubal infertility.

Research

Numerous research questions arise from this review, many of which were identified in the sections on *C. trachomatis*, *N. gonorrhoeae*, and PID. Studies of particular importance to infertility include the following:

- 1. more definitive epidemiologic studies in Canada on the etiology of infertility, the role of known and silent episodes of PID, the specific contribution of *C. trachomatis* and *N. gonorrhoeae*, the potential of other pathogens to initiate disease or further its progress, and the risk factors for tubal infertility;
- 2. studies to determine if aggressive treatment of PID with corticosteroids prevents tubal injury from PID and results in improved fertility outcome; and
- 3. studies to determine if *C. trachomatis* persists as a viable organism in tubal epithelium after infection and short courses of treatment, and to see if more aggressive long-term courses of treatment should be evaluated.

Acute Epididymo-orchitis

Introduction

The epididymis is a sausage-shaped structure attached to the testicle. It consists of a single tubule about 3.5 m long that is coiled on itself. The epididymis transports sperm and also provides additional unspecified factors to the sperm that enable it to be motile and to fertilize an ovum. Inflammation of the epididymis, or epididymitis, is common. Frequently, the testicle is involved as a contiguous structure.

Etiology

Epididymitis associated with urethritis is usually due to N. gonorrhoeae or C. trachomatis. Although a variety of other organisms, most of which are not sexually transmitted, have been associated with epididymitis, they are all much less common. In older men, non-sexually transmitted pathogens, including those responsible for urinary infection, also often cause epididymitis. Escherichia coli is the most common cause.

Illustrative Case - Pain in the Scrotum

Randy is a 22-year-old moving van driver. He has had no serious illness and is currently well. He was referred because a routine urinalysis done as an employment requirement disclosed pus cells.

The physician did not take a sexual history. He did obtain a urine culture and also a urethral swab culture for N. gonorrhoeae. Both cultures were reported to be negative. Randy was informed that the pus cells in his urine were insignificant and no further investigation was required. Urinalysis was normal.

Three weeks later Randy developed an acute epididymitis with marked swelling of his epididymis, scrotal pain, and fever. He was treated with cephalexin. After three days he had not improved. A repeat urethral swab with a specific request for C. trachomatis and N. gonorrhoeae was done when he checked himself into an emergency room. Five days later he was informed that his urethral culture was positive for C. trachomatis. Treatment with doxycycline resulted in gradual improvement over the next two weeks. However, he continued to have discomfort in his scrotal sac and discomfort with intercourse for the next six months.

Although no sexual history was taken during his care, the public health nurse contacted Randy after receiving notice of the positive culture. Upon questioning, he readily admitted to numerous sexual contacts. He has one regular girlfriend with whom he shares an apartment. However, during the past year he has had at least 15 other sexual contacts and his lifetime experience approaches 50. Although he often carries condoms, he uses them only if his sexual partner requests it. His regular girlfriend takes oral contraceptives and they seldom use a condom. As far as he knows, his girlfriend is not aware that he has other sexual contacts during his travels away from Toronto.

On further history, his girlfriend has sought medical help on at least three occasions with urethritis or lower abdominal pain. At no time has she had cultures for C. trachomatis and no diagnosis has been made. She has been treated with a vaginal preparation with some response.

Randy missed a month of work and during his absence his position was terminated.

Illustrative Case (cont'd)

Learning Points

- Many physicians are not aware that asymptomatic pyuria in men is a common presentation for *C. trachomatis* and for *N. gonorrhoeae*. Simple tests to detect pyuria in men are proving to be a major intervention point in identifying those who require further investigation and treatment for either or both pathogens.
- Many care providers do not realize that C. trachomatis will not be diagnosed unless specific requests are made for identification of this pathogen in urethral swabs or swabs taken from other sites. In this instance, both Randy and his girlfriend failed to have a diagnosis made and inappropriate treatment was prescribed. This led to serious health complications for both.
- Few care providers take a sexual history from their patients. If this had been
 done, Randy's physician would probably have been alerted to the possibility
 that he might have a STD, specifically chlamydia. Patients are usually willing
 to share their sexual history with caregivers, particularly if they have a genital
 health complaint.
- Many people with STDs get most of their care from emergency room or walkin clinics; they are not part of a comprehensive health care system. As a result, there is a failure of diagnosis due to reports not being seen by care providers and a failure of prevention.

Epidemiology

Epididymitis is common. In the military it accounts for more days lost from service than any other illness. Probably 30 000 men each year in Canada see their physician for this illness. In about one-half of the patients, sexually transmitted pathogens, specifically *N. gonorrhoeae* and *C. trachomatis*, are responsible.

Clinical Manifestations

Epididymitis usually has a sudden onset with severe scrotal pain. A preceding history of urethritis or urethral discharge may be present. The overlying scrotum may be red and edematous.

Diagnosis

A gram stain and culture of urethral exudate or scrapings should be routine. In addition, an aspirate of the epididymis for culture will often provide a specific pathogen as an etiologic agent.

Sequelae

Infertility secondary to epididymitis is rare in Canada, if both epididymides are involved. Bilateral epididymitis occurs in less than 2% of men with acute epididymitis. Probably fewer than 100 men each year in Canada are at risk of permanent infertility from bilateral epididymitis with scarring of both epididymides.

Treatment

A combination of anti-microbial agents effective against both *N. gonorrhoeae* and *C. trachomatis* should be initiated in all patients with epididymitis if it was likely to have been sexually transmitted. Usually, the response is relatively rapid with resolution over 5 to 10 days. Patients rarely need to be admitted to hospital.

Prevention

The prevention of sexually transmitted epididymitis due to $\it N. gonorrhoeae$ and $\it C. trachomatis$ is based on the same premises as other illnesses due to these pathogens. Primary prevention programs should be effective if patients with asymptomatic infection are screened and treated. Secondary prevention with adequate treatment of an initial urethritis may occasionally prevent the subsequent episode of epididymitis. However, epididymitis often occurs simultaneously with urethritis.

Male Infertility

Information on male infertility is lacking in many respects. Over the past two decades, some sexually transmitted pathogens have been associated with male infertility, but their contribution is currently considered to be quite small.

Sexually transmitted pathogens have been thought to cause male infertility in the following situations:

- Epididymitis with subsequent scarring and obstruction of semen flow through the epididymis. Because it is rare for epididymitis to occur bilaterally, it is a rare cause of sterility.
- Subacute infection due to *C. trachomatis* or *N. gonorrhoeae* or other sexually transmitted pathogens in the prostate or genital tract resulting in lowered fertility as measured by a "low sperm count." This has been postulated in some instances, and patients are often treated with an antibacterial agent such as tetracycline to determine if treatment will improve the sperm count and increase fertility. However, evidence for improvement is not substantial.
- Sexually transmitted infections may rarely involve one or both testes and produce permanent damage as a result of inflammation with fibrosis and scarring.
- In the pre-antibiotic era, *N. gonorrhoeae* occasionally produced ongoing urethral fibrosis with urethral strictures and urethral obstruction. In the last 30 years, this has been rare, and many physicians have never seen a urethral stricture due to a sexually transmitted pathogen.

At present, less than 5% of male infertility is probably due to known sexually transmitted pathogens. Although other agents may be transmitted

through intercourse that can cause reduced male infertility, this is unproven and remains speculative.

Abortions

Spontaneous abortions are extremely common, and in some studies almost one-half of conceptions fail to survive to mid-pregnancy. Most spontaneous abortions are of unknown etiology. Many are genetic in origin, with serious chromosomal abnormalities responsible for the failure of continuing fetal development. However, some are due to infection with sexually transmitted pathogens. In Canada, presumably less than 1% are in this category.

Globally, syphilis is the most common sexually transmitted agent responsible for abortion. Other pathogens associated with spontaneous abortions include HIV-1 and cytomegalovirus. *C. trachomatis, N. gonorrhoeae*, genital herpes, and human papillomaviruses have not been proven to cause spontaneous abortion, and their contribution, if any, to this complication

of pregnancy is negligible.

Some women have recurrent spontaneous abortions, whose cause cannot usually be identified. Tests to exclude syphilis should be performed routinely in all patients who have spontaneous abortions, since it is the only known infectious treatable cause of abortion. Although some investigators have concluded that *Ureaplasma urealyticum* can cause recurring abortion, others have not found this association.

A therapeutic abortion or any procedure that goes through the cervix into the uterus can be associated with invasive upper genital tract infection, if the patient has gonococcal or chlamydial cervical infection. In some studies, the prevalence of chlamydial cervicitis is about 20% in patients who have therapeutic abortions. This population is at high risk of acute PID with the sequelae of infertility and ectopic pregnancy if the diagnosis of chlamydia or gonorrhoea is not considered and treated at the time of pregnancy termination. The risk of developing PID post-abortion is higher in adolescents than in older women.

Prematurity

Definition

Prematurity is defined as a birthweight of an infant less than 2 500 g. It is usually a result of pre-term delivery but can be due to intrauterine growth retardation.

In industrialized societies, prematurity occurs in 5% to 8% of pregnancies. Over one-half of all perinatal deaths follow premature birth. Premature births are costly. In the United States it has been estimated that if premature infants had been delivered as healthy term infants, the savings in 1990 would be about \$1 billion. When these figures are

extrapolated to Canada, premature births cost at least \$100 million to the Canadian health care system.

Etiology

The proportion of premature births due to infection is uncertain. However, several studies have shown that between 30% and 50% of premature births are associated with chorioamnionitis. Chorioamnionitis is an important cause of premature rupture of fetal membranes. Chorioamnionitis can cause fever and abdominal pain, but is not associated with any recognized symptoms in about one-half of women who present with this condition. Although the exact proportion is uncertain, between 10% and 20% of premature births may be associated with sexually transmitted infections. Lower genital tract infection with *N. gonorrhoeae*, *C. trachomatis*, and probably other bacterial pathogens may lead to inflammation in the chorion and the placenta. Inflammation leads to weakening of the membranes and ultimately to rupture and premature labour. Some evidence has suggested that premature labour may be mediated by prostaglandins produced by these bacteria in the chorion.

Several factors have been associated with premature labour and the resulting prematurity. They include: positive cervical cultures during the last half of pregnancy for either or both *N. gonorrhoeae* and *C. trachomatis*, bacterial vaginosis, sexual intercourse during the last two weeks before labour, and positive cultures for *Ureaplasma urealyticum*.

Prematurity is also commonly associated with perinatal infection. Two-thirds of all perinatal infections and the resulting mortality occur in premature infants. A considerable proportion of this morbidity and mortality had its onset prior to delivery with spread of infection from the chorion to the fetus.

Treatment

The results of several studies have suggested that immediate administration of antibacterial regimens will prevent premature delivery in some patients. The studies are preliminary, and it is still unknown if all patients who have premature labour should be prescribed antibiotics.

Prevention

Primary prevention of STDs through programs identified in other sections of this monograph will significantly reduce prematurity.

Programs to screen, diagnose, and treat sexually transmitted infections during pregnancy can also be effective. Routine risk assessment with screening for syphilis and culture for *N. gonorrhoeae* and *C. trachomatis* in populations at increased risk can be cost-effective.

Other areas require further study. The use of condoms during coitus during the last half of pregnancy deserves further study.

Sexual Abuse and STDs

Canadian society is becoming more aware of sexual abuse. Although for obvious reasons it is difficult to get accurate estimates, between 1% and 2% of female children probably are sexually abused. Obviously, some abuse occurs as a result of rape by strangers; however, most is done by members of the child's household. Preliminary studies have suggested that people who abuse children are more likely to be infected with sexually transmitted pathogens, so that a significant proportion of children (perhaps 10% to 20%) who are sexually abused are at substantial risk of acquiring STDs (Schwarcz and Whittington 1990).

Epidemiology

If a mother is infected, sexually transmitted pathogens are frequently transmitted at birth. Viral infections including HIV, hepatitis B, herpes simplex, and presumably human papillomavirus may be transmitted at birth and only become evident months or years later. This also applies to syphilis. On the other hand, children over two years of age who have gonococcal infection, chlamydial infection, or *Trichomonas vaginalis* should be evaluated for sexual abuse. Although inanimate objects may be blamed for infections occurring in children, there is no scientific evidence for transmission of infection from such articles as toilet seats and towels.

In January 1987, the Laboratory Centre for Disease Control of Health and Welfare Canada began a nation-wide survey of STDs in sexually abused minors. In the first year, 11 reports of STDs in children who had been sexually abused were received from 3 of 19 participating centres (Table 15).

Table 15. Surveillance of Sexually Transmitted Disease in Sexually Abused Minors

STD/pathogen	No. abused	Sex
Gonorrhea	4	F
Genital Warts	4	F*
Genital Chlamydial Infection	1	F
Trichomoniasis	1	F
Gardnerella vaginalis	1	F

^{*} One male case reported.

Source: Canada, Health and Welfare Canada, "Sexually Transmitted Disease in Canada, 1987," Canada Diseases Weekly Report 15 (Suppl. S2) (April 1989).

Management

STDs in children require specialist investigation and intervention. The infections must be treated immediately to prevent long-term complications from the pathogens for which curative therapy exists. Persons with specialized training are required to interview the patient, determine the likelihood of sexual abuse, and make decisions about further investigation.

Cervical Neoplasia

Definition

Cervical dysplasia (or cervical intraepithelial neoplasia) is common, and of uncertain malignant potential. However, it appears to occur in the same population of patients who have invasive cervical cancer. Cervical dysplasia is usually diagnosed on the basis of cervical cytology.

Invasive cervical cancer can be occult and evident only on histologic examination or can be apparent on cervical examination.

The risk factors appear to be similar for each of these abnormalities, and most experts consider them to be a continuing spectrum of neoplastic disease, presumably due to the same etiologic factors.

Epidemiology

Worldwide, cervical cancer is the second most common cause of death due to cancer in women, and in many countries it is the most important cause of cancer-related deaths. About 20% of all invasive cervical cancer occurs before the age of 40.

Cytologic changes consistent with cervical intraepithelial neoplasia are reported in between 2% and 10% of women seen in STD clinics. Cervical intraepithelial neoplasia is less common (< 1%) in women attending family practice or prenatal clinics.

The incidence of invasive cervical cancer varies from less than 2 per 100 000 in Jewish women in Israel to a high of 80 per 100 000 in Brazil. In Canada, the incidence of invasive cervical cancer is between 5 and 10 per 100 000 per year.

Etiology and Risk Factors

The etiology of cervical neoplasia has been controversial, but the epidemiologic evidence is now substantial and supports human papillomavirus as the cause. A variety of types have been identified by molecular technologies in the neoplastic cells. Types 16 and 18 are the most commonly associated with invasive cancer. The following have been consistently shown to be risk factors for invasive cancer: multiple sexual partners or a partner who has many other sexual partners, early onset of sexual activity, cigarette consumption, and other STDs, including herpes simplex virus, HIV, *C. trachomatis*, and bacterial vaginosis.

Links to Infertility and Suboptimal Pregnancy Outcomes

Invasive cervical cancer is treated by radiation with or without hysterectomy. Cervical intraepithelial neoplasia is treated by local biopsy excision, conization, followed by cryotherapy. Laser treatment is increasingly used.

Following destructive cervical procedures, cervical stenosis or incompetence occurs in a significant minority of patients. This can result in infertility (about 5%), early loss of pregnancy with spontaneous abortion (about 5%), and premature labour. Although such complications are important, they are secondary to the cure of the neoplasm. Cure rates between 95% and 99% are usually achieved.

Prevention

Primary prevention involves strategies to ensure that women do not become infected with papillomavirus. Secondary prevention involves screening with cervical cytology (Pap smear) for early diagnosis of cervical dysplasia, careful follow-up, and ultimately locally destructive measures to remove neoplasia.

Research Priorities

Research priorities for cervical neoplasia include the following:

- 1. Epidemiologic studies to determine the risk of cervical neoplasia after papillomavirus infection and further proof of the causal role of this virus in cervical cancer are necessary.
- 2. The molecular biological basis of human papillomavirus transformation of normal cells to malignant cells needs to be fully understood.
- 3. Effective strategies to prevent human papillomavirus infection are still not available.
- 4. No therapies effective for treating human papillomavirus infection are known. Treatment regimens to cure this infection are urgent.
- 5. Research into the interaction of human papillomavirus with other STDs, especially HIV, is needed.

Neonatal and Congenital Infections

In Canada in 1991, prenatal care is available to most pregnant women. In many health care settings, care includes screening programs for some STDs and neonatal ophthalmic prophylaxis at birth. As far as we know, no national registry records STDs in neonates and infants. As a result, our estimate of infections in Canadian neonates and infants will be extrapolated from U.S. data and from personal observations.

The sexually transmitted pathogens that may be transmitted during pregnancy or at birth to the newborn are listed in Table 2, Part 1. In this section we will not discuss the consequences of prematurity itself. This is obviously a major adverse neonatal outcome, but no specific sexually transmitted pathogen is usually transmitted to the premature infant. In this section, we will focus only on specific infectious syndromes in the infant.

The overall frequency in a given population group varies depending on risk factors in the mothers. We would estimate that in most areas of Canada, less than 1% of newborns are infected with a sexually transmitted pathogen that they have acquired from the mother. However, there are populations at markedly increased risk in whom between 2% and 3% of infants are infected. Overall, of the approximately 500 000 infants born in Canada in 1991, probably between 3 000 and 10 000, or 1 in 50, will acquire a sexually transmitted infection from their mother that will create acute or chronic illness. It should be apparent from the data that control efforts to limit the spread of STDs and eradicate these illnesses are worthwhile.

Specific Syndromes

Ophthalmia neonatorum is a classic illness that was recognized to be transmitted from mother to infant in the last century. Effective prophylaxis with silver nitrate was initiated by Crede, an effective regimen that is still continuing. Topical silver nitrate prevents over 90% of gonococcal infection of the conjunctiva and about 60% to 70% of eye infection due to C. trachomatis. It remains extremely important for use in groups at increased risk of either of these pathogens.

Without prophylaxis, over 50% of infants born to women with gonococcus of the cervix will acquire ophthalmia neonatorum; about 35% of mothers with C. trachomatis in the cervix will transmit the infection to the eyes of their infants. In both instances, conjunctivitis develops. Gonococcal conjunctivitis occurs within the first week of life and can rapidly progress to keratitis and destruction of the eye. Chlamydial conjunctivitis is a much more benign disease with onset usually in the second week of life as a subacute illness.

If diagnosed early, both illnesses can be treated with effective antimicrobial regimens. At present, few long-term ocular consequences result from these pathogens in infants in Canada, due to the combination of prophylaxis and effective treatment for chlamydial conjunctivitis. Due to concerns about chemical conjunctivitis, efforts have occasionally been made to discontinue routine ocular prophylaxis in Canadian hospitals. Although this may be considered for individuals at very low risk of STDs, it is inappropriate for those at higher risk. Ultimately, screening programs during pregnancy along with education and treatment of those at increased risk may be more effective.

Acute Invasive Illness in the Newborn

Group B streptococci, *N. gonorrhoeae*, and occasionally *Ureaplasma* urealyticum and *Mycoplasma hominis* can cause acute illness in infants. These infections are far more common in premature infants than in full-term infants. At present, Group B streptococci are the leading cause of neonatal sepsis and neonatal meningitis. As discussed earlier, Group B streptococci are not necessarily always sexually transmitted, and the epidemiology of these pathogens is poorly understood. Neonatal sepsis is relatively common and occurs in almost 1% of neonates. However, organisms proven to be transmitted sexually likely account for less than 5% of neonatal sepsis in Canada today.

Overall, neonatal sepsis is of major concern because of its high mortality and morbidity, particularly if associated with meningitis, which often leads to permanent neurologic sequelae. Early recognition of infants who are failing to thrive and immediate initiation of anti-microbial therapy

have improved the outcome of these infections.

Congenital Viral Infections

Herpes simplex virus, cytomegalovirus, and HIV are transmitted sexually and may cause neonatal infection.

Herpes simplex has infected between 10% and 20% of Canadian mothers, but transmission to infants rarely occurs. However, when transmission to infants does occur, it is always serious and associated with life-threatening illness, which can be complicated, can be obscure, and can have variable presentations. The disease should be considered in differential diagnosis by health care providers who care for neonates. With the availability of specific treatment with acyclovir, early recognition and treatment of herpes simplex are a priority. The long-term sequelae of infants who survive herpes infections are predominantly neurologic.

Cytomegalovirus can also infect infants and may present a variable picture. This was described more fully in Part 2. Cytomegalovirus should be considered in infants who appear to have neonatal sepsis and in those who have a variety of congenital syndromes, including microcephaly (small heads) and other neurologic diseases. Most infants born with cytomegalovirus infection appear to be healthy and do reach their long-term potential as children and young adults. However, studies are ongoing to assess further the impact of this virus on human potential when trans-mitted from mothers to their infants during pregnancy or at birth.

Worldwide, hepatitis B is the pathogen transmitted most frequently from mothers to their infants. However, in Canada, programs have been established in most regions to diagnose hepatitis B carriage in mothers and to institute prophylaxis at birth to prevent transmission to infants. Such programs are important and relatively cost-effective despite the low incidence of hepatitis B in pregnant women in Canada. In many countries, resources are generally not available to provide screening programs and

prevention programs. As a result, people migrating to Canada from these countries often are hepatitis B-positive.

Hepatitis B rarely causes serious illness in the newborn but may in childhood or early adult life lead to cirrhosis or to carcinoma of the liver.

HIV is discussed in detail as a childhood disease in Part 2.

Congenital Syphilis

Congenital syphilis as a serious sexually transmitted neonatal infection has been discussed in Part 2. It also has to be considered in all infants who have neonatal sepsis and infants with a variety of congenital abnormalities. It is easily diagnosed if specific studies are done and is rare in Canada today. Less than 100 infants were likely born in Canada with congenital syphilis in 1992. However, due to the recent increase in congenital syphilis in the United States, we must remain vigilant and encourage women to seek prenatal care, continue to be screened for syphilis, and be treated if seropositive.

Prevention of Neonatal Infections Due to Sexually Transmitted Pathogens

Excellent care programs instituted by physicians and supported by federal and provincial government initiatives and a variety of non-government organizations have led to Canada's overall record as a nation in which most infants are born healthy, with no limitations on their potential due to sexually transmitted infections. However, considering that as recently as 1922 over 10% of children entering school in Glasgow, Scotland, had congenital syphilis, the need for continuing vigilance is evident. Such precautions include:

- 1. primary prevention programs continually reinforced and supported throughout Canadian society, identifying principles of prevention discussed in Parts 1 and 5;
- 2. specific programs incorporated into prenatal programs to include screening for syphilis, hepatitis B, and, perhaps, chlamydial infection, to diagnose, treat, and prevent such infections in fetuses and newborns: and
- 3. early recognition and treatment in newborns by ensuring that physicians are knowledgeable and competent in this area of neonatal care.

Despite reasonably high quality programs in Canada, substantial room still exists to reduce the overall disease burden of these infections in newborns further, perhaps by as much as 50% by the year 2000.

Artificial Insemination and STDs

Several important sexually transmitted pathogens have been transmitted by semen insemination programs. Despite this, few studies have been done on the risk to women who undergo artificial insemination.

In 1989, Barratt et al., in a review of 32 centres in the United Kingdom, found that no screening procedures were routine other than HIV serology. Once individuals had entered the program, only in a very few centres were they asked about changes in sexual partners or any risky sexual behaviour. In one study, Tjiam et al. (1987) found that *C. trachomatis* was present in 6.3% of 237 semen donors and *Ureaplasma urealyticum* in 35.9%. Concern has also been raised about the transmission of cytomegalovirus and hepatitis B virus. The number of infants born by therapeutic insemination in Canada is unknown, but it is probably about 1 000 each year. Each conception is the result of an average of 6 inseminations, with a range up to over 100. Some institutions have, in the past, mixed the semen of multiple donors before administration.

Transmission of HIV by donor insemination has merited special attention because of its documented occurrence in several recipients of artificial insemination. Strict guidelines have been developed by the American Fertility Society, which include the exclusive use of frozen semen and negative HIV serology in the donor at least six months after the last

semen contribution.

To our knowledge, no studies have been published on the practices of artificial insemination in Canada. Data on what standards of practice have been established or are being followed are urgently needed.

Artificial insemination is an important reproductive technology that enables some women to be mothers. Rigid control of donor recruitment and both serological and cultural studies to ensure that donors have no sexually transmitted infections are essential to reduce to zero the likelihood of transmitting pathogens that could compromise the health of the mother or infant. In 1991, this includes screening the donor for HIV, cytomegalovirus, hepatitis B virus, *C. trachomatis, N. gonorrhoeae*, syphilis, and, perhaps, *Ureaplasma urealyticum* and *Trichomonas vaginalis*. At present, no tests are available to screen for human papillomavirus in men. All semen should be frozen for six months and donors retested to ensure that donors are not carrying HIV. Donors who have multiple sexual partners or participate in unsafe sexual practices should be excluded from donor programs.

Part 4. Contraceptives and Sexually Transmitted Diseases

Introduction

Contraceptives are generally used to prevent unintended pregnancies, but some can protect against STDs. Contraceptive use and choice of product are determined by the preference of the individual along with the mutually shared concerns of the couple. Some factors involved are perceived risks of STDs or pregnancy; perceived undesired consequences

of STDs or pregnancy; availability of the method; cost; acceptance by the sexual partner; perceived safety of the method; and timing within the menstrual cycle.

A couple's sexual activity and contraceptive use are also influenced by gender relationships, with the man often determining the conditions under which sexual intercourse occurs. Other important social norms include: community peer pressure, religious proscriptions against a particular contraceptive, and the gender power relationships within society.

Although some contraceptives protect against both pregnancy and STDs, both policy and service delivery have focussed largely on preventing pregnancy. However, the contraceptives most effective and most widely used for preventing pregnancy have the least impact on preventing STDs. Often, the man assumes major responsibility for the use of the condom, the contraceptive that has the best record for preventing STDs.

STDs and unplanned pregnancies share many similarities:

- Genital intercourse is associated with both. 1.
- 2. Both STDs and unplanned pregnancy discriminate against women, who bear the most health risks associated with outcomes of intercourse.
- Younger populations, particularly women under the age of 25, 3. have the highest levels of both unintended pregnancies and STDs. The level rises substantially for socially disadvantaged women.
- In most societies a woman's status depends largely on her role as 4. a wife and mother. In the gender imbalance common to most societies, a woman may have limited control of sexual relations and contraceptive practice. As a result, she may have little choice about exposure to STDs. The ultimate effect on her fertility and subsequent rejection by society as a woman unable to reproduce are paradoxical.

Reproductive health care for women is currently fragmented within the health care system. Family planning, ante-natal care, and sexual health are not usually provided within one continuous care structure. Although this has not been well studied within the private sector in Canada, in the public health sector it has been shown that women do not receive adequate reproductive health care and counselling. Risk assessment surveys in family-planning clinics show that at least one-quarter of women are at risk of STDs. In STD clinics, over one-half of women are not using contraceptives despite histories of STDs and unplanned pregnancies.

These overlapping needs provide unique opportunities to deliver welldesigned, broadly based reproductive health programs to women at their point of contact with the health care system. In Canada, the private sector provides over 90% of reproductive health care to women. Unfortunately,

Illustrative Case — Contraceptives Don't Necessarily Prevent STDs

Marlene is a 24-year-old surveyor who is employed by a mining company in northern Canada. She is currently seeking care because of recurring lower abdominal pain, severe dysmenorrhoea, and irregular prolonged menses. She dates the onset of these symptoms to a vague illness that commenced about three months earlier.

Marlene has had one pregnancy, which was terminated during the third month. She has twice been prescribed oral contraceptives. However, after several months she discontinued their use because of severe headaches. Two years ago, after the therapeutic abortion, she persuaded a physician to insert an IUD. At no time was her sexual health or the measures necessary to prevent STDs discussed.

Over the past seven years since she became sexually active, she recalls eight different sexual partners. With each boyfriend, she has had an ongoing relationship for between six weeks and six months. To her knowledge she has had no sexually transmitted infections. However, when questioned she gave a history of some abnormal vaginal symptoms, which included increased discharge and, on occasion, moderately severe pain with intercourse. Although her partners on occasion have used condoms, use has been inconsistent, and she estimates that at least 70% of coital episodes have taken place without a condom. Pelvic examination disclosed moderate cervicitis with pain on cervical motion. There was also pain on deep palpation in the left cul-de-sac.

Laboratory investigation, including cultures from the cervix, showed that Marlene had an infection with C. trachomatis. Subsequent treatment of this infection with tetracycline improved some of her symptoms.

On return visit, the IUD was removed and she was educated on strategies to request sexual partners to use condoms and encouraged to limit the number of partners.

Learning Points

- Health providers need to incorporate sexual education and suggest safe sexual practices at the time they prescribe contraceptives. Too often this does not occur.
- IUDs in several studies have been associated with an increased possibility of PID, particularly in women who have more exposure to STDs because of "high-risk partners."
- C. trachomatis is particularly insidious and frequently responsible for atypical symptoms within the upper genital tract that may not be recognized to be due to a sexually transmitted pathogen. As a result, specific therapy may not be provided.
- The patient should have been given information on the risks of ectopic pregnancy and tubal infertility as a result of the PID. Consistent efforts by health care providers and the media to link infertility to these pathogens may be an important strategy to assist Canadians at increased risk to identify initiatives to reduce this risk.

among women at greatest risk — sexually active adolescents and socially disadvantaged women — reproductive health care is deficient in meeting the basic needs of care and counselling. The increasing concern about the heterosexual spread of HIV and the link between STDs and infertility should provide an additional stimulus to facilitate a merger of care programs targeted to female reproductive health.

Specific Contraceptive Methods

Oral Contraceptives

The influence of oral contraceptives on genital tract infections is complicated and not completely understood. Most studies have shown a substantially increased risk of cervical infection with *C. trachomatis* among oral contraceptive users than among control groups using barrier contraceptive methods (Harrison et al. 1985). This increase is significant and may be one of the reasons for the number of chlamydial infections occurring in Canada. The biological basis for this is not fully explained, but it may be due to the increased area of the cervix containing columnar epithelium that occurs in women on oral contraceptives. C. trachomatis preferentially infects columnar epithelium.

Of equal importance is the influence of oral contraceptives on upper tract invasion. Some studies have suggested that women on oral contraceptives are much less likely to have PID (Washington et al. 1985; Wølner-Hanssen et al. 1990). This seems to be true for both chlamydial and gonococcal PID. The protection seems to occur only in women who have been on oral contraceptives for 12 months or longer, and it disappears when usage is stopped. Also, the occurrence of tubal infertility is not increased among women with a history of oral contraceptive use (Cramer et al. 1987). Despite the increased incidence of chlamydial cervicitis in women on oral contraceptives, this infection does not seem to lead to silent PID and subsequent tubal infertility. The mechanisms for the protective effect or oral contraceptives on upper genital tract invasion by chlamydia and gonococci are unknown.

Additional studies have also suggested that chlamydial PID, when it occurs in women using oral contraceptives, is less severe (Wølner-Hanssen 1986).

Oral contraceptives are a possible risk factor for the acquisition of HIV infection in women. Although controversial, the most definitive studies have suggested that, after exposure to HIV, women on oral contraceptives have an increased risk of infection compared to those not taking them (Plummer et al. 1991).

Intrauterine Devices

Few studies have been conducted on women using IUDs. No evidence has surfaced that IUDs predispose to infection with C. trachomatis or N. gonorrhoeae. However, the incidence of bacterial vaginosis in IUD users may be four to eight times higher than in non-IUD users. Bacterial vaginosis has not been proven to be sexually transmitted, and its etiology remains obscure. It may be associated with suboptimal outcomes of

pregnancy, including prematurity.

Initial studies suggested that the incidence of PID in IUD users was four to eight times greater than in non-users (Gump et al. 1983; Aral et al. 1987). Other studies have revealed that the risk of PID among IUD users is probably far less, between one and one-half and two times greater than among non-IUD users (Cramer et al. 1987). Most of these infections occur at the time of IUD insertion. The role of STDs in this increased risk is significant. Also, one type of IUD, the Dalkon shield, has shown an increased risk for women to develop both PID and tubal infertility in U.S. studies. STDs and multiple sexual partners were both independent risk factors in these studies. On the other hand, copper IUDs used by women with only one sexual partner had no increased risk of tubal infertility. Also, some studies have shown that the risk of acquiring HIV infection is increased among IUD users independently of other risk factors.

Much more research is needed to determine further the association and potential role of IUDs in PID and tubal infertility (Kessel 1989). In the meantime, women at risk of STDs should be encouraged to use contraceptive measures other than IUDs. Although the data remain confusing with regard to the role of IUDs in upper tract infection, no evidence shows that IUDs protect women from any STD, including HIV.

Condoms

Latex condoms protect men and women against STDs. Although the quality of the data is suboptimal, the results of some studies have suggested that gonococcal infection and genital herpes are much less common among women whose sexual partners use condoms regularly (Stone et al. 1986). However, the evidence is much stronger that condom use in men protects against gonococcal infection and chlamydial infection. No evidence has been found that condom use protects against human papillomavirus.

PID and tubal infertility both seem to occur less often in women whose sexual partners use condoms for contraception (Cramer et al. 1987). These U.S. studies provide good evidence for encouraging the use of condoms in relationships in which STDs may be transmitted.

Several studies have also provided evidence that condoms are effective in preventing the heterosexual transmission of HIV in either direction.

Factors that result in condom failure to prevent either STDs or pregnancies are poorly understood. Studies have suggested that condom breakage occurs in between 1% and 3% of coital episodes (Trussell and Kost 1987). Proper storage of condoms and educational methods for proper use are essential.

No condoms for women in particular are in widespread use at the present. Continuing investigation to design and field-test an appropriate condom that can be controlled by women should be a high priority.

Spermicides

Spermicides are often combined with diaphragms for contraceptive purposes. Spermicides have excellent antibacterial and anti-viral activity against a variety of STDs. Several studies have shown that the use of a spermicidal agent and a diaphragm will markedly reduce the prevalence of gonococcal infection, trichomonas, and genital herpes. The efficacy for chlamydial infection is less certain, although in one study cervical gonococcal infection was reduced by 24% and chlamydial cervical infection by 22% (Quinn and O'Reilly 1985). Although in one study PID has been shown to be reduced by the use of spermicides, tubal infertility was not reduced among users of spermicides alone (Cramer et al. 1987). When combined with a diaphragm there was a sharp decrease in tubal infertility.

Spermicides, when combined with barrier methods of contraception, particularly the diaphragm, will effectively reduce the incidence of STDs and the resulting sequelae. However, further studies are needed.

Surgical Procedures

Tubal ligation protects against PID. However, obviously it has no effect on the acquisition of STDs in the cervix or vagina, and people at risk of STDs need to continue to use alternative methods to reduce their risk of acquiring STDs and HIV.

Therapeutic abortions and presumably septic abortions are far more often associated with endometritis and other symptoms and signs of upper tract invasion if patients have cervical infection with either gonococci or chlamydia. The risk appears to be about three times as great.

Presumably, any procedure that requires instrumentation of the cervix should be done only in patients without cervicitis or cervical infection. In most instances, cultures for *C. trachomatis* or *N. gonorrhoeae* should be done before cervical manipulation. Although good studies have not been conducted, anti-microbial prophylaxis possibly should be used routinely if transcervical procedures must be done before microbiologic studies to exclude women who are at risk of sexually transmitted infections.

Conclusions

Women need to consider their goals carefully both in family planning and in STD prevention when they choose contraceptives. Trade-offs may be necessary. Ideally, couples should consider dual methods of contraception and STD prevention to achieve high-level protection against both pregnancies and STDs. Hormonal contraceptives are the most effective single reversible method available to prevent pregnancy. Female and male sterilization also are effective in preventing pregnancy; however, they are not readily reversible. None of these methods prevents the transmission of STDs. On the other hand, spermicides and mechanical

barrier methods, including condoms, reduce the risks of most STDs. They are coital dependent and, to a considerable extent, their use is determined by men. Behavioural variables are important to ensure that these technologies are available, used appropriately, and acceptable to both

partners.

The prevention of STDs requires optimal use of contraceptives during coitus among people who are at increased risk of transmitting STDs. The issues raised by contraceptive use are complex, and additional research is needed to understand the social, behavioural, and biological factors that are required to ensure that optimal contraceptive and disease prevention strategies are used in Canada.

Part 5. Strategies for the Prevention of Sexually Transmitted Diseases and Their Consequences in Canada

Overview of Canada's Health Care System

Canada has a health care system that ranks among the best in the world from the perspective of both the patient and the caregiver. The fundamental principles of universality, portability, unhindered access, and comprehensive care are available to all Canadians. In addition, an expensive bureaucracy has been avoided and administrative costs are less than half those of many other industrialized countries. It continues to provide individual patients with a choice of caregivers.

The Canadian health care system also is increasing its commitment to disease prevention. Due to both federal and provincial leadership in this area and significant contributions from organizations such as the Canadian Public Health Association, numerous strategies are reducing the impact of many illnesses related to lifestyle choices and those due to occupational and environmental hazards.

Despite these generally favourable observations, the Canadian health care system is under considerable stress because of an aging population and increasing ossification of many parts of the system. Resistance to change, lack of information on outcomes of treatment, wide dissemination of treatment before proper evaluation, managerial inefficiencies, discontinuity of care, ineffective leadership, an absence of risk-taking initiatives, and an over-dependence on traditional patterns of care all impair the ability of our health care system to adapt for its changing role in the next decade.

Provision of Care in Canada Related to STDs

Sexually transmitted infections are cared for by a variety of health personnel. Special treatment facilities for STDs are provided in about one-half of Canadian cities with a population of more than 100 000. The

effectiveness of these centres is controversial. Many patients prefer not to seek care from a specialized clinic where attendance is stigmatized by a probable association with STDs. On the other hand, such clinics often have become models for the efficient provision of care and resources for education and research on STDs. However, even in cities in which highly organized clinics provide effective services, less than 15% of the patients receiving care for STDs are seen in this setting. Probably about 50% of STDs are cared for in the offices of primary care physicians, from 10% to 20% by gynaecologists and other specialists, and from 10% to 15% by nursing units in remote areas. To our knowledge, no one has reviewed the source of care for patients with STDs in Canada; thus, these figures are approximate.

We need good health service studies on the quality of STD care and patient satisfaction in a variety of settings. From studies in the United States we know that less than 10% of physicians do adequate routine assessment of STD risks or educate patients with regard to sexual health or the prevention of STDs. Presumably, this is an area in which effective leadership with well-designed programs could improve patient care through the education and motivation of physicians and other health care providers.

In some areas, deficiencies are apparent in the organization and provision of health care as it pertains to STDs:

- 1. We have lacked federal resources for the study of infectious disease epidemiology, including STDs. As a result, most of the disease prevalence or incidence data are fragmentary and are not amenable to meaningful analyses. We are frequently not in a position to determine the disease burden or able to design and evaluate effective control programs.
- The development and implementation of federally funded control 2. programs are inadequate: in most instances, we have not set national goals for disease control or developed national programs to provide federal leadership to all provinces in the control of infectious diseases, including STDs. The Laboratory Centre for Disease Control, Health and Welfare Canada, is committed to STD control, but it is underfunded for the development of national STD control programs. Most initiatives for the control of infectious diseases, including sexually transmitted pathogens, are the responsibility of the provinces, with consequent variable responses and resource commitment.
- Remote communities of indigenous people and the urban poor 3. are not well served for a variety of reasons.
- The direct costs of IVF are high in relation to its current success 4. rate of about 15% to 20%. Therefore, for STDs and their sequelae of infertility, a health care system that is driven by curative

medicine to the neglect of prevention will result in the cost of care being an unnecessarily large drain on limited resources.

Health Research

Canada's health research program has evolved during the past 30 years with federal leadership through the Medical Research Council and the National Health Research and Development Program. In 1991, the two agencies provided almost one-half of the \$540 million allocated to Canadian scientists to investigate health issues. Over 95% of all health scientists are based in universities or hospital institutions. Almost all federal and most provincial funds for health research are provided on the basis of competitive grants to individual scientists after peer review. Only a small proportion of federal or provincial research funds are allocated to targeted programs. One exception is the AIDS program of the National Health Research and Development Program, which has allocated over \$20 million to this disease since 1986. A significant proportion of Canada's health research dollars comes from the non-governmental sector, which gives funds to targeted diseases, including cancer, heart disease, multiple sclerosis, diabetes, and many others. These agencies collectively provide over \$100 million annually to health researchers. With the exception of HIV/AIDS, no agency targets any infectious disease and specifically none of the sexually transmitted infections. Also, no agency targets reproductive health for research funding.

Intervention Strategies

The Role of Government

Former Prime Minister Pierre Elliott Trudeau stated "government has no role in the bedrooms of its citizens." Although most Canadians would accept the truth of this dictum, it does not exempt federal and provincial governments from assuming a major responsibility for the control and prevention of STDs throughout Canadian society.

From our perspective, this would include:

1. Surveillance to include ongoing data collection, analysis, and use to monitor progress in achieving specific control targets for all STDs. Surveillance is a powerful tool to convince society of the importance of STDs. It is essential to use resources appropriately and to document the effectiveness of specific interventions. Canada has a good, but not outstanding, record in data analysis and application. However, unevenness in data collection across the provinces has made it difficult for Canadian statistics to be useful. These statistics are not amenable for evaluation of prevention by control programs. Epidemiologic investigation of

- disease patterns or outbreaks is also essential to establish risk profiles and identify disease reservoirs.
- 2. Provision of specialized laboratory facilities nationally and within provinces to conduct more sophisticated investigation of STD pathogens. This includes a variety of essential initiatives, such as (a) national standards and quality control to ensure that laboratories throughout Canada are identifying sexually transmitted pathogens appropriately; (b) studies of pathogen susceptibility to anti-microbial agents; and (c) monitoring trends in evolving or changing characteristics of pathogens. Laboratory Centre for Disease Control has an ongoing program to address these initiatives for gonococcal infections and has started similar programs for chlamydia, syphilis, and hepatitis B viruses.
- Guidelines for the management and prevention of STDs. Such 3. guidelines have been developed by the federal government with input from health professionals and the provinces. They should be effectively disseminated to all health care providers with a substantial effort to monitor their usefulness. The federal government undertook initiatives in this area in 1988-89 and in 1992 and is updating these guidelines.
- Education programs for the general public and for targeted 4. groups. The federal government has considerable expertise in health education and health promotion. Programs to promote self-esteem and provide individuals, especially women, with more control over their sexual and reproductive health would be more effective than narrowly focussed programs on safer sex. Integration of social and economic programs that address the problems of poverty, street youths, and drug addiction with education programs on the primary prevention of STDs and the linkage of STDs to infertility is a priority.
- STD and HIV prevention programs should be combined in both 5. federal and provincial jurisdictions. The separation of these initiatives was unwise and has led to duplication of efforts and less effective use of resources.
- Research and training. Training future researchers, supporting 6. current investigators, and facilitating ongoing research programs are largely the responsibility of government agencies, particularly the Medical Research Council and the National Health Research and Development Program. Research funded during 1990-91 throughout Canada is detailed in the Appendix. In the summary, we have categorized research by diseases and pathogens. Canadians have made and continue to make important contributions to the knowledge of sexually transmitted pathogens.

However, the overall proportion of research funding that is applied to either basic fundamental or applied clinical aspects of STDs is a negligible proportion of the total funding available. In particular, there was no funding identified in 1990-91 for either gonococcal infection or syphilis. These two pathogens continue to be important causes of disease in Canada and deserve continuing support as a research priority. Also, the kind of research and training within university institutions influences attitudes of health care providers and so influences the standards of patient care. It is important, therefore, that reproductive health care be dealt with appropriately in training.

Role of Non-Government Organizations

The Canadian Public Health Association (CPHA), the Canadian Medical Association (CMA), and several other agencies have taken important initiatives in an effort to prevent STDs. The CPHA and the CMA have an extensive network of health care providers who can be both educated and motivated to focus activities in these areas. Prevention needs to be emphasized by (1) innovative ideas to enhance women's health (an area that has been generally underfunded); and (2) facilitating synergy in prevention strategies, particularly between contraception and STD prevention, and ensuring that the care providers and the Canadian public are well informed about such preventive measures. In this regard, the Canadian Infectious Diseases Society in its brief to the Royal Commission on New Reproductive Technologies (July 24, 1990) made a very credible suggestion that "to convey the concept that oral contraceptives do not protect against the acquisition of sexually transmitted diseases, individual containers of oral contraceptives should include a condom. Since the vast majority of women who use oral contraceptives are sexually active, inclusion of a condom could hardly be construed to promote sexual activity." This kind of initiative accompanied by a well-written short message could rapidly educate most sexually active women in Canada about the need for additional protection beyond contraceptives, if they have reason to be concerned about personal risk of STDs.

Other non-government organizations could be considered as essential groups to become involved in the prevention of STDs. Educational associations at all levels need to develop material that conveys healthy sexuality appropriate for the culture and age. Numerous examples are currently available where value systems can be incorporated through involvement of parent-teacher associations or other groups to ensure that cultural and religious sensitivities are considered in planning Canadianwide initiatives on STDs. Federal support for such initiatives would likely be cost-effective.

Other groups, such as university students, may require additional information. Presumably, these groups can be targeted through such

avenues as university health care facilities, the university media, and peerdeveloped programs.

Role of the Media

During the last five years the media has done a commendable job with its education of the general public regarding HIV/AIDS. However, other STDs have not received the priority they deserve. The Canadian public would probably read, watch, or listen to information on sexual health and STDs; most people are interested in their own sexual health and have a concern and interest about STDs in general. The audio-visual media tend to downplay sexual fulfilment and satisfaction within monogamous relationships, and often depict frequent partner change as normal and necessary for sexual happiness. This statement is obviously controversial. On the other hand, we would urge that it be discussed within the context of "the media's role in determining the norms for sexual behaviour in Canada." The links between STDs and PID, infertility, and ectopic pregnancy could be projected more effectively within the news media and by the film industry.

Programs for High-Frequency Transmitters

Core groups of STD transmitters have been previously identified as the reservoir of transmission and often the source of STDs. Strategies are needed to assist individuals in these groups to recognize and reduce their risk of acquiring STDs; ensure that when infection occurs it is rapidly treated before it produces complications or is transmitted to new partners; and acquire a sense of self-worth and have better control over their own lives. Education through non-judgmental messages as part of an overall program is also needed to encourage those who have multiple partners to change their lifestyle.

Few resources have been put into these kinds of programs in Canada or elsewhere. Such programs would likely be cost-effective in substantially reducing the number of people who are transmitting STDs, particularly *N. gonorrhoeae, C. trachomatis*, HIV, and *T. pallidum*, to others. In the province of Manitoba, the chlamydia control program is probably responsible for the decrease in incidence of chlamydia (Manitoba, Manitoba Health 1991). The incidence of chlamydial PID also appears to be decreasing. Further studies with program implementation should be considered for these groups where they can be identified throughout Canada. Both men and women should be targeted for intervention.

The Swedish Experience

From 1970 to 1989 a dramatic decline in gonococcal and syphilis incidence occurred in Sweden (Danielsson 1990); the number of cases has fallen 25-fold, and now both syphilis and gonococcal infections are rare. Sweden leads the world in this regard, but many other countries in Northern Europe are also observing rapid reductions in these sexually transmitted infections. Although multiple factors are considered to be

responsible for this trend, several have been identified as particularly important:

- improved treatment regimens with health care provider education to use them appropriately;
- increased use of condoms for casual sex due in part to the education programs associated with HIV/AIDS prevention;
- liberal treatment of contacts without necessarily demanding laboratory confirmation of infection; and
- screening programs for asymptomatic women and men.

The impact on *C. trachomatis* has been less dramatic; however, during the last five years substantial progress has been made, and the prevalence and incidence of *C. trachomatis* infection have been reduced by 50% or more in some Swedish counties and cities (Thejls et al. 1991). The focus of this program includes the above initiatives and:

- screening and treating large numbers of women who are considered to be at increased risk because of sexual exposure.
 This includes women who are obtaining contraceptive care, pregnancy termination, prenatal care, and treatment of other STDs; and
- contact tracing and treatment of male partners of these women.

These two measures combined with widespread education programs for the public and for health care providers with special programs for youth counselling services are having a substantial sustained impact on the transmission of *C. trachomatis*. In Sweden and in other northern European countries, major initiatives are now under way to use the information gathered and to develop programs that will control and reduce, perhaps by tenfold, the incidence of *C. trachomatis* in their populations.

Preliminary studies done during 1990 have suggested that as a result of the effect of these control programs on gonococcal and chlamydial transmission, the incidence of PID has decreased by more than 50% (Weström 1988). This decrease is presumed to be the direct result of these control programs. Although it is too early yet to determine the impact of these programs on ectopic pregnancy, infertility, and chronic pelvic distress syndromes, it is probable that these sequelae will also decline rapidly over the next five years with the success of the gonococcal and chlamydial control programs.

In Canada, initiatives to reduce all STDs, including HIV, through primary prevention have been shown to be effective. For those individuals who become infected, there are federal and provincial guidelines to ensure that health care providers seek specific diagnoses and initiate effective treatment. Further transmission of infection is minimized through contact tracing and treatment of sexual partners. Although resources for contact tracing are variable across Canada, the traditional approach of provision of

diagnostic services, contact tracing, and effective treatment has led to a dramatic decrease in the incidence of gonococcal infection in Canada in the last decade. However, due to the lack of symptoms and long-term carriage of chlamydial infections, present control programs that do not screen individuals at increased risk have only limited impact on chlamydial prevalence and long-term sequelae.

Chlamydia screening programs are now readily feasible. Laboratory screening tests are sensitive, specific, and widely available to all Canadian women. Numerous studies have identified risk factors for the acquisition of chlamydial disease. Thus, screening programs can be prioritized to target individuals at particularly high risk of acquisition and transmission of chlamydial infection.

In the province of Manitoba, where chlamydial screening technology was made available to physicians in the early 1980s, an increasing number of physicians have taken advantage of its availability to screen those of their patients who might be at risk.

This screening program combined with other control initiatives described above have had a substantial impact on the prevalence of chlamydial infection in populations, with an overall 30% reduction in the number of chlamydial infections during the 1980s. Of greater interest is the impact on the sequelae of chlamydial, infections. PID has fallen dramatically in Manitoba over the period 1984-1990, with a reduction of over 50% in individuals hospitalized with PID, and a concurrent reduction in non-hospitalized PID patients of over 40%. These parallel reductions in direct health costs certainly more than pay for the laboratory and physician-related costs of the control program in Manitoba. Further economic analysis of these data is necessary in order to determine the probable leverage of a dollar spent in chlamydial control on the total health budget. Almost certainly, the long-term sequelae, including tubal infertility and ectopic pregnancy, will also now begin to decline.

This experience in Manitoba compares favourably with the Swedish experience with chlamydia control programs. It also substantiates the tentative cost-benefit data collected from mathematical modelling of chlamydia control programs in the United States.

Chlamydia control programs are feasible and cost-beneficial. Political leadership, along with sustained advocacy and support from epidemiologists, health organizations, and communities at risk, are now needed to ensure that our knowledge is implemented and that the sequelae of chlamydial infections — chronic pelvic pain, recurring PID, infertility, and ectopic pregnancies — are rapidly reduced.

Conclusions

Lessons can be learned by other countries, including Canada, from the success of the Swedish interventions. We do not have to accept passively the current incidence of gonococcal, chlamydial, or other sexually transmitted infections. Effective, reasonably inexpensive control initiatives can

quickly reduce the incidence of these infections and, in turn, reduce their sequelae.

Appendix. STD and AIDS Research Funding, 1990-91

Summary of STD and AIDS Research Funding, 1990-91

Pathogen/STD	No. projects	Amount (\$)
AIDS	107	5 648 554
Other STDs*		
Herpes virus	4	262 421
Cytomegalovirus	2	132 950
Chlamydia	6	333 397
Human papillomavirus	8	395 082
Chancroid	3	149 030
Hepatitis B	2	51 248
Ureaplasma	1	56 000
Total	26	1 380 128**

^{*} In 1990-91, there was no funding from government agencies allocated to projects directly related to PID, ectopic pregnancy, or reproductive illness as a consequence of STDs. Support for these types of projects often comes from pharmaceutical or diagnostic companies.

** Excluding AIDS funding.

Note: Total health research funding is \$540 million. Funding for non-AIDS STD research is 0.26% of health research funding.

STD Research

B.C. Health Care Research Foundation

Sexual assault

\$21 196

B.C. Health Development Fund — Joint Research Grants
Human papillomavirus detection — Cervix

\$102 600

Health and Welfare Canada

	Alary, Michel — Laval (Comparison of amoxicillin and erythromycin	\$105 756
	in the treatment of genital infection of pregnant women) Arbuckle, Tannis — Concordia (Long-term sequelae and traumagenic factors in childhood sexual abuse)	\$16 200
	Bowie, William R. — British Columbia	\$55 466
:	(Understanding sexually transmitted disease/AIDS risk behaviour in adolescence: an in-depth analysis of the Canada Youth and AIDS Study and data set)	
1	Brisson, Jacques — Laval (Risk factors for human papillomavirus type 16 lesions of the uterine cervix, a case-control study)	\$25 470
	Cameron, William — Ottawa	\$22 030
	(Interaction of <i>H. ducreyi</i> and HIV in natural human infection)	
	Cohen, Marsha M. — Manitoba	\$2 090
	A population-based study of cervical screening	
	in Manitoba)	Φ10.40 7
	Delage, Gilles — Montreal Évaluation de la durée à long terme de l'immunité	\$16 487
	contre le virus de l'hépatite B suite à l'immunisation	
	active-passive combinée du nouveau-né)	
	Feldman, William — Ottawa	\$635
- (The mental health sequelae of childhood sexual abuse:	
(s there a dose response curve between severity and type of abuse and sequelae?)	
	Hollett, Joan E. — New Brunswick	\$1 331
(Formulation project and evaluation of a community-based child abuse treatment model)	
	Millson, M.E. — Toronto	\$38 000
(Proposal for community health intervention monograph: evaluation of contact tracing and management of contacts in STDs and AIDS/HIV infection)	
	Preiksaitis, Jutta K. — Alberta	\$79 273
1	Cytomegalovirus seronegative blood components for the prevention of primary cytomegalovirus infections in children with malignant disease)	
(Scott, Elizabeth — Hamilton A systematic overview of the effectiveness and cost effectiveness of contact tracing and partner notification in controlling STDs)	\$40 000

112 Understanding Infertility

Sobsey, R.J. — Alberta (Development of treatment guidelines: sexual abuse	\$25 561
and assault of disabled victims) Villeneuve, J.P. — Montreal (Porteurs asymptomatiques du virus de l'hépatite B)	\$34 761
MHRC	
McClarty, Grant, and Robert Brunham (The thymidylate cycle of chlamydia)	\$34 400
MMSF	#0 ₹ 000
Alfa, Michelle	\$27 000
(H. ducreyi) Taylor, Patrick (Screening for human papillomavirus DNA in men: control of disease transmission through donor insemination)	\$37 500
MRC	
Copone, John P. — McMaster (Studies on herpes simplex virus and mammalian cell gene expression and function)	\$57 681
Johnson, David C. — McMaster (Role of membrane glycoproteins in immune surveillance of herpes simplex virus infections)	\$66 537
Loh, Lambert C.H. — Saskatchewan	\$53 677
(Molecular biology of cytomegalovirus infections)	
McClarty, Grant — Manitoba	\$68 137
(Reduction of ribonucleotides in Chlamydiae) McDermott, Mark R. — McMaster	φ <u>τ</u> ο οοο
(Mucosal vaccination against herpes simplex virus type 2)	\$59 203
McNicol, Patricia, Robert Brunham,	
and Fernando Guijon — Winnipeg	\$59 420
(HPV and uterine cervical neoplasia) Pater, Alan and Mary — Newfoundland (Glucocorticoid-dependent oncogenesis of primary cells	\$59 376
by human papillomavirus) Robertson, Janet A. — Alberta	φ <u>ε</u> ς 000
(Characterization of <i>Ureaplasma urealyticum</i>)	\$56 000
Sacks, Stephen — B.C.	\$79 000
(Non-invasive diagnosis of herpes viral infections)	7.000
Shirley, James R. — McMaster (Expression of human papillomavirus type 16 genome in cultured cells)	\$53 492

Tsang, S. Siug — British Columbia	\$55 134
(Enhancement of human papillomavirus DNA induced cell transformation)	
Wenman, Wanda, and Kaul Ravi	\$60 019
(Pathogenesis of human chlamydial infections)	Ψ00 013
Special Projects	
Plummer, Frank (AIDS, approx. \$277 600)	
Ronald, Allan (Chancroid, approx. \$100 000)	\$477 600
Brunham, Robert (Chlamydia, approx. \$100 000)	
Ontario Ministry of Health	
Sellors, John, et al.	\$36 520
(Chlamydial risk screening of women at	+ 0 0 0 2 0
birth control clinics)	
Sellors, John, et al.	\$34 321
(Detecting chlamydial urethritis in males)	
AIDS Research	
Quebec Health Foundation	
HIV	\$60 000
AIDS treatment	\$520 580
Human retrovirus	\$46 032
Health and Welfare Canada	
Adrien, Alix — Montreal	\$16 730
(Évolution des connaissances, attitudes et	
comportements de la communauté haïtienne du Québec	
face aux facteurs de risque du SIDA)	411 500
Aye, Mauney T. — Ottawa (A correlative and longitudinal study of brain and	\$11 500
immune system disease in HIV infection: a	
feasibility study)	
Camerman, Norman — Toronto	\$24 170
(Structure determinations of anti-AIDS agents)	
Chan, Voon-Loong — Toronto	\$67 500
(Reverse transcriptase and anti-viral therapy in AIDS)	400 400
Church, Deirdre L. — Calgary (Pilot study: the gastrointestinal tract in HIV)	\$32 400
Coates, Randall A. — Toronto	\$212 563
(A prospective study of male sexual contacts of	Ψ212 000
individuals with AIDS-related complex or AIDS)	
Coates, Randall A. — Toronto	\$69 623
(The Ontario HIV seroprevalence study in women of	
reproductive age)	

Elmslie, Thomas J. — Ottawa (The impact of HIV/AIDS in the general and family	\$10 782
practice setting) Elmslie, Thomas J. — Ottawa (Assessment of sexual behaviour related to transmission	\$8 501
of HIV infection among women in the primary care setting) Fanning, Mary M. — Toronto (Validation of a quality life instrument for patients	\$14 000
with HIV infection)	
Fanning, Mary M. — Toronto	\$44 210
(A prospective study to define disease status and prognostic indicators in HIV infection in a clinical	
practice setting)	
Filion, Lionel G. — Ottawa	\$76 746
(Immune functions of HIV-infected monocytes)	ΨΙΟΙΞΟ
Fridland, Judith F. — Toronto	\$1 280
(Study to assess the relationships among social support,	Ψ1 200
coping, and quality of life for people with AIDS:	
development phase)	
Gallop, Ruth — Toronto	\$10 500
(A longitudinal study to test the relative effects of	
four adjuncts to knowledge-based education for	
care-providers working with AIDS patients)	
Gill, John — Calgary	\$47 000
(Evaluation of anti-viral drugs in HIV infection in vitro)	
Goldman, Hyman — Montreal	\$23 318
(Neural and thymic cell cultures — the study of AIDS)	
Gornitsky, Mervyn — Montreal	\$18 130
(A clinical and laboratory longitudinal evaluation	
of the oral health complications of patients with AIDS)	
Grover, Steven A. — Montreal	\$41 733
(The natural history of symptomatic HIV infection	
and the costs associated with hospital care)	
Grover, Steven A. — Montreal	\$11 512
(The costs of hospitalizing patients with AIDS)	
Hammond, G.W. — Manitoba	\$21 081
(An evaluation of methods for improved detection of HIV)	
Hankins, Catherine A. — Montreal	ΦE 100
(Risk factors for HIV infection among incarcerated	\$5 100
women)	
Hankins, Catherine A. — Montreal	\$78 852
(Examination of the feasibility of a seroprevalence	Ψ10 00Z
study of HIV antibody in childbearing women)	
-	

Hart, Geraldine A. — Dalhousie (Exploratory study of the support needs of	\$34 950
haemophiliacs with AIDS and their families)	+00 -00
Henderson, J. Frank — Alberta (Metabolism and toxicity of anti-HIV dideoxynucleosides)	\$33 729
Hiscott, John — Montreal	\$87 830
(Molecular anti-viral strategies in the development of	
AIDS therapies)	400.000
Hudson, James B. — British Columbia (Evaluation of plant thiophenes and quinones as	\$30 000
anti-AIDS virus compounds)	
Izaquirre, Carlos A. — Ottawa	\$8 000
(Prospective immunological studies in a cohort of	
haemophiliacs with and without antibodies to HIV)	4170.000
Joly, Jean R. — Montreal (Étude de seroprévalence du VIH dans un	\$170 000
réseau d'hopitaux sentinelles au Québec)	
Jophi-Sukhwal, Sathna — Toronto	\$48 800
(Retroviral vector development to confer resistance	,
against HIV-1)	
King, Alan — Queen's	\$79 562
(Survey of Canadian youth re AIDS knowledge, attitudes and behaviours)	
Kleiman, Lawrence — Montreal	\$23 200
(Structure and metabolism of HIV-1 primer t-RNA)	φ23 200
Klein, Ami — Toronto	\$57 000
(Isolation and characterization of lymphocytic	
compound found in plasma of AIDS/ARC patients)	
Lamothe, François — Montreal	\$51 863
Coates, Randall A. — Toronto	
(Prevalence and incidence of HIV-1 and HIV-2 infection in parenteral drug users in Montreal and Toronto)	
Lapointe, Normand — Montreal	\$83 563
(Mode de transmission de l'infection HIV de la mère	Ψ00 000
à l'enfant)	
Lau, Allan S.Y. — Toronto	\$174 190
(Interferon regulation of the immune system in AIDS)	40 770 4
Long, Bonita — British Columbia	\$3 724
(Self-esteem, social support, hemophobia, and coping strategies of gay men with HIV)	
MacFadden, Douglas K. — Toronto	\$27 922
(The natural history and early detection of	,
central nervous system dysfunction in patients with	
HIV-related disorders)	A EC 0.55
Mak, Tak W. — Toronto (Functional effects of HIV and HIV related proteins)	\$53 011
(Functional effects of HIV and HIV-related proteins)	

Mak, Tak W. — Toronto (Transominant repressors of HIV regulatory proteins	\$183 5	500
tat and rev) Matthews, Fred — Toronto	\$53 9	926
(HIV-infected young people: a needs study) McCarthy, Gillian M. — Western Ontario (A feasibility study of head and neck lesions in patients with HIV infections)	\$2 2	298
McDonald, J.R. — Calgary (HIV positive blood transfused population identification and impact assessment: feasibility study)	\$3 (085
Menezes, Jose P. — Montreal (Immunovirological evaluation of HIV-seropositive individuals and patients with AIDS)	\$31.5	500
Mills, E.L. — Montreal (HIV-mediated immunosuppression of phagocytic cells)	\$58 6	557
Millson, M.E. — Toronto (Evaluation of a program to prevent HIV infection in injection drug users in Toronto)	\$73 9	962
Murphy, M. — Vancouver	\$9 (000
(Individuals with AIDS who are at home) Myers, Ted — Toronto (A small group intervention for the prevention of AIDS	\$26 3	300
in homosexual and bisexual men) Ornstein, M.D. — York (Analysis of knowledge, attitudes, and behaviour	\$13 8	800
regarding AIDS among Canadian adults) Osterland, C.K. — Montreal (AIDS-associated defects in the cellular and molecular physiology of B lymphocyte activity)	\$34 ()54
Pajurkova, E.M. — Calgary (The neuropsychological aspects of HIV)	\$19 1	107
Parivali, M.A. — Montreal (Structure-function relationships in the expression of HIV-1 reverse transcriptase activity)	\$54 4	100
Pekovic, Drasko D. — Laval (Studies of lymphocyte destruction in HIV-positive patients)	\$2 8	370
Pepler, Carolyn — Montreal (Nurse-patient interaction with the terminally ill AIDS patient in palliative and acute care settings)	\$1	24
Plummer, F.A. — Manitoba (Perinatal transmission of HIV infection and paediatric AIDS)	\$20 (000

Poon, M.C., et al. — Calgary/McGill/ Saskatchewan/British Columbia	\$30 340
(Heterosexual transmission of HIV: haemophiliacs) Prevec, Ludvik A. — McMaster (Human adenovirus-based expression vectors for HIV virus antigens)	\$14 369
Qualtiere, Louis F. — Saskatchewan (HIV infection of neurological tissue)	\$14 963
Read, Stan — Toronto (Molecular genetic heterogenicity of HIV-1	\$2 620
isolates and disease progression) Read, Stan — Toronto (Studies on the relationship of sequential HIV	\$22 200
immunoblots, p24 antigen capture and clinical outcome in a cohort of 120 haemophiliac children)	
Remis, Robert S. — McGill (Study of HIV seroprevalence among women undergoing abortion in Montreal)	\$44 460
Rice, George P.A. — Western Ontario (Interaction of HIV and cytomegalovirus in immune	\$36 630
and nervous systems) Ridway, A. — Western Ontario (HIV regulatory genes)	\$46 460
Romanowski, B., et al. — Edmonton/Montreal/ British Columbia/Manitoba	\$22 310
(Canadian collaborative study of HIV infection among sexually active women)	
Rosenthal, K., and D.G. Harnish — McMaster (Role of t-cell mediated immunity and virus replication on HIV-induced disease progression)	\$97 634
Ruedy, John — British Columbia/Calgary/McGill/ Toronto	\$86 572
(Multicentre Canadian azidothymidine trial) Ruedy, John — British Columbia (Oral corticosteroids for pneumocystis carinii	\$10 668
pneumonia in AIDS) Salit, Irving E. — Toronto	\$5 006
(Corticosteroid therapy for AIDS) Sarazin, F. — Victoria (Pouchalogy in AIDS)	\$267
(Psychology in AIDS) Schechter, Martin T. — British Columbia (The Vancouver lymphadenopathy AIDS study)	\$30 000
Sehon, A.H. — Manitoba (Immunological strategy for arresting the development of AIDS in asymptomatic HIV-infected individuals)	\$60 000

Sekaly, Ragick — Montreal	\$26 960
(Molecular and immunological strategies for	
the generation of vaccines against HIV)	
Sekla, L.H. — Manitoba	\$149 000
(The Manitoba study: HIV seroprevalence in	
individuals, STD, IV drug users and healthy persons	
screened for syphilis)	
Smith, MaryLou — Toronto	\$52 519
(Behaviour and HIV infection in children)	
Sommerville, M. — Montreal	\$124 600
(Legal, ethical, social, and economic issues	
raised by AIDS)	
Soto, Julio C. — Montreal	\$2 828
(Le SIDA et le contrôle des infections au Québec: étude	
des attitudes, des connaissances et des comportements	
des intervenants en santé dentaire)	
Szewczuk, M.R. — Queen's	\$5 000
(Serological determination of anti-id. antibody and	
its role in AIDS)	
Taggart, M.E. — Montreal	\$21 910
(Exploration de certains besoins fondamentaux	
de parents d'enfants SIDAtiques en appartenant à	
des familles à risque)	
Taylor, Kathryn — Toronto	\$13 968
(Physician response to AIDS)	
Taylor, Kathryn — Toronto	\$3 500
(Impact of AIDS on health care providers)	
Thibodeau, Lise — Laval	\$79 875
(HIV immunosome as a novel approach for a	
subunit vaccine against AIDS)	
Toma, Emil — Montreal	\$5 390
(Therapy for AIDS)	
Verhovsek, H. — Ottawa	\$19 252
(Concerns, coping and adjustment of individuals	
following notification of HIV-positive or negative status)	
Wainberg, M. — Montreal	\$229 892
(Development of an antigen detection assay and	
a neutralization assay for TLV-III)	
Weaver, M. — British Columbia	\$2 118
(Determinants of retrovirus activation in	
HIV-seropositive individuals)	
Wegman, T.G. — Alberta	\$33 800
(Cytokine regulation in the placenta: implication	
for perinatal AIDS)	

Johnson Tarismitted	mections 119
Woo, S.K. — Toronto	\$45 001
(A brief screening test for cognitive	410 001
defects in HIV infection)	
MRC	
Butterworth, R.E. — Montreal	\$42 345
(Wernicke's encephalopathy in AIDS patients treated	Φ42 343
with azidothymidine)	
Camerman, N. — Toronto	\$31 250
(Structure determinations of anti-AIDS agents)	φ01 200
Dekaban, Greg A. — Western Ontario	\$59 900
(The development and understanding of immune	,
responses to HTLV-I)	
Forsdyke, Donald R. — Queen's	\$60 000
(Role of lymphocyte G _o /G _I growth regulatory genes	
in AIDS)	
Gervais, Francine, and Emil Skamene — McGill	\$47 483
(Genetic control of susceptibility to murine AIDS)	
Gupta V. Sagar — Saskatchewan	\$40 298
(Chemotherapy of AIDS: studies on heterocyclic	
derivatives of phosphone formate)	\$00 =00
Jolicoeur, Paul — Montreal	\$68 768
(Molecular studies on HIV)	ф 7 0.400
Mak, Tak — Toronto (HIV: mechanism of cell kill)	\$79 400
Prevec, Ludvik A., et al. — McMaster	\$47 350
(Human adenovirus-based expression vectors	φ47 000
for immunodeficiency virus antigens)	
Sekaly, R.P. — Montreal	\$80 200
(Molecular basis for the immuno-deficiency	,
observed in AIDS patients)	
Wainberg, Mark — Montreal	\$68 138
(Studies on drug-resistant variants of HIV-1)	
Special Projects	
Berstein, Alan, et al.	\$83 200
(Viral inhibition therapy against AIDS)	Ψ00 200
Kang, C.V. — Ottawa	\$73 000
(Development of a candidate vaccine against AIDS)	, , , , , ,
Rosenthal, K., et al. — McMaster	\$64 000
(Identification of relevant T-cell epitopes of HIV	
for generation of an effective vaccine for AIDS)	
Ontario Ministry of Health	
Myers, Ted, et al. — Toronto	\$49 024
(Survey on HIV infection for First Nations people)	4.0 021
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It is our hope that an increasing awareness of the importance of STDs will lead to effective initiatives to curtail this epidemic.

Hope, societal improvement, education, and continuing research are all essential ingredients of any recipe for the curtailment of STDs. We continue to urge government to give leadership and encourage everyone to become involved in a sustained and significant effort to reduce the impact of these illnesses on society.

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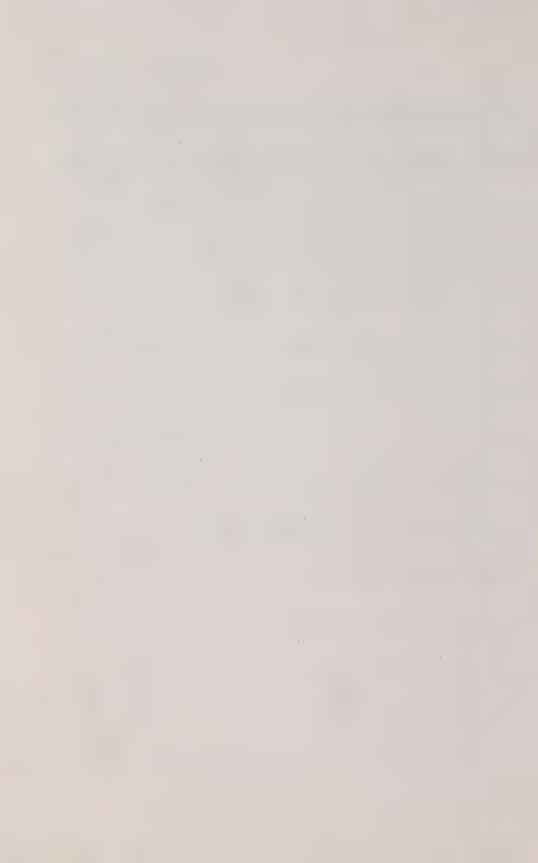
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The Physiological Effects of Aging on Fertility Decline: A Literature Review

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Executive Summary

This paper provides a review of the literature concerning the physiological effects of aging on fertility. Two general themes are developed: the chronological age beyond which there is a substantial risk of infertility and the causes of fertility decline.

Three types of studies have examined the effects of age on fertility. Demographic studies show the broad effects of age on fertility, but do not permit differentiation of causal factors. Information on women receiving artificial insemination provides a population in which variation in fertility is due to only intrinsic factors. The third type of study is the examination of the population with unexplained fertility decline in the reproductive function due solely to age. This is referred to as true biological aging, and the paper reviews the explanations of this phenomenon. In addition to biological aging, the status of the reproductive system is influenced by cumulative infertility factors, such as sexually transmitted diseases, pelvic inflammatory disease, and occupational hazards. Finally, the effect of advancing age on fetal outcome and maternal survival is reviewed.

Introduction

An increasing number of Canadian couples marry and start having children later in life. In 1970, 12 percent of all women in their thirties who gave birth to a child were first-time mothers. This figure increased to 26 percent in 1986.¹ By 1990 this figure rose to 29.6 percent for women aged 30-34 and 23.6 percent for women aged 35-39.² The major question that this trend raises is whether couples — and women in particular — are compromising their ability to procreate by postponing childbearing. Studies of societies exhibiting natural fertility³ clearly show that as women age there is a longer waiting time to conception. It is obvious that people expect to live well past their ability to reproduce. But what does the scientific literature say about the ending of ability to reproduce? What are the physiological mechanisms that are involved in this process?

Most experts agree that the first crucial studies examining the relationship between age and reproduction took place in the early 1980s. These studies gave rise to a spate of review articles, in which the authors examined the relevant literature and almost unanimously determined that there were certain cutoff ages beyond which reproductive impairment occurred and that various biological (intrinsic) and cumulative (extrinsic) infertility factors were responsible. However, there was no consensus concerning the age at which the decline in fertility occurs in men and women, nor was there agreement on the particular factors that cause the decline.

Two sets of factors are implicated in age-specific infertility.⁴ The first comprises those factors involved in "true biological aging," aging due to changes in the organs of the reproductive system and the chemical messages that coordinate their behaviour. The other set of factors centres around daily living. The additional stresses to which the reproductive system is subjected include exposure to environmental or occupational hazards, extended contraceptive use, exposure to sexually transmitted diseases (STDs), conditions of the reproductive tract such as endometriosis, psychogenic factors, drug abuse, smoking, and iatrogenic causes.

The effects of true biological aging and of the cumulative exposure to infertility-related factors may both be reflected in the physiology of the reproductive system. It is inadequate to examine only the contribution from true biological aging as the other factors that may affect complicated reproductive systems also need to be taken into consideration.

The physiological health of the reproductive system may be measured by looking at various end-points in the reproductive process. These include the ability to conceive, carry a viable child to term, and give birth to a child free from congenital defects.

When the literature on infertility was reviewed, the array of definitions that were used was striking. Words such as infertility, sterility, subfecundity, and fertility had different meanings depending on the

authority used.⁶ The medical community and demographers use a definition for infertility that is based on the time period required for conception to occur.⁷ A second term, subfecundity, is used in the literature to describe an increase in the time required to conceive.⁸

In this paper, reproductive impairment pertaining to the ability to carry a child or to give birth to a child free from congenital defects is included in the definition of infertility because, in practical terms, having a child is the desired goal. For the purposes of this paper, no specific time criterion has been imposed in this definition of infertility. The term "sterility" simply refers to the inability to ever have a child. Fertility, therefore, means the ability to conceive, carry, and give birth to a child free from major congenital defects.

Many review papers written in the 1980s took the view that couples, and women in particular, who delayed childbearing were putting their ability to procreate at risk. They implied that there was scientific evidence for certain cutoff ages, after which point there was a marked increase in infertility. They cited various biological and cumulative infertility factors as being responsible. This paper reviews the major studies that led these authors to their conclusions to determine if there is scientific evidence to clarify the relationship between chronological age⁹ and increased fertility risks in men and women. It also examines the physiological effects of aging on the reproductive system.

Methodology

The study began with a collection of review papers from the 1980s. The key factors affecting fertility were identified by the frequency with which they were mentioned in the literature. Studies from 1980 to May 1991 that dealt with each factor were then searched using MEDLINE. As well, various papers were pulled using MeSH subject headings. This search strategy was supplemented by adding review papers collected by the Royal Commission on New Reproductive Technologies and review papers commonly cited by the authors of original studies. Where the number of review papers published on a topic was large, papers representing conflicting points of view were included and the remainder cited as references. In cases where many studies on a specific topic reached the same conclusion, the most recent papers were directly included in the review and the remainder cited.

Studies from Canada, the United States, and Europe were covered, with Canadian data included whenever possible. Papers were selected for discussion from the abstracts provided by MEDLINE and, when these were not available, from the discussion sections of recent works. This method also recovered unique, older papers that were pertinent.

MEDLINE includes papers in all languages, but 75 percent are in English. Because an initial search revealed that over 90 percent of the articles on the topic of infertility came from Canada, England, Sweden, Denmark, the United States, Germany, and France, and as these countries report in English, later searches were restricted to papers in English.

The Literature Review

Two themes emerged from the literature on aging and infertility, and these formed the basis of the review. The first involved determining ages beyond which there is a substantial risk of infertility. This basically meant determining the age at which a sharp decline in fertility occurs. The second theme arose from studies concerned with the causes of fertility decline. The studies looking at the age question were often unclear, because they simultaneously tried to discover when the decline occurs, what the causes of the decline were, and whether the decline was caused by intrinsic or extrinsic factors. Despite external factors, such as exposure to disease, infection, or environmental hazards, having a possible effect on the physiology of the reproductive system, these authors were concerned only with reproductive impairment that resulted from increased age. 12 However, this aspect is difficult to isolate, as the longer a person lives, the longer the exposure to various hazards, so both occur concurrently. Many of these were population studies and the authors did not have data regarding the environment in which persons lived, nor data concerning their general health. 13

In a woman of childbearing age, infertility is considered to be a reflection of the physiological health of the reproductive system, which in turn is affected by age and other factors that may cause changes. The studies concerned with fertility decline looked at key end-points within the reproductive system functioning that are sensitive to age and also to other factors. To perform these studies measurable end-points were required, including: the inability to conceive, the occurrence of miscarriage (spontaneous abortion), and the occurrence of congenital defects.¹⁴

Determining When Age Becomes a Factor in Declining Fertility in Men and Women

Three approaches were identified that were used to determine when age becomes a factor in declining fertility. These were: demographic studies; studies that focussed on artificially inseminated women; and studies of that segment of the population suffering from unexplained infertility. Each type of study made a contribution to an understanding of the relationship of age to declining fertility.

Demographic Studies

Demographic (or population) studies provide the broadest overview of the effect of age on infertility. They are used to examine infertility because it is necessary to know what relationship fertility has to age as a baseline. Data are required from a large number of persons who have lived through and passed the reproductive age. Population studies report on the length of time to conception (derived, for example, from comparisons of marriage and birth records), the time between conceptions (from birth records), or rates of sterility. However, data are not available on the rate of miscarriage as it was not reported in the historical records — historical populations are studied because birth control and voluntary sterilization were not used to control fertility. However, they did have poorer medical care and different social and nutritional milieux. This means that it is necessary to look also at modern populations that have benefited from modern health care and that practise natural fertility. ¹⁵

The best source of demographic data would be modern populations, because they are subject to the current extrinsic factors. However, it is impossible to use their marriage records and birth records to look at age-related infertility, as most couples artificially limit their fertility. Questionnaires have been used to derive data from modern populations by a few researchers. Pregnant women have been questioned about their medical and reproductive histories, including the length of time required for conception. But even these studies may have serious limitations; for example, it is difficult to separate the effects of male age from those of female age, because spouses are often of similar age. Also, demographers have to deal with incomplete data, as the couples they review have not necessarily finished having their families.

On the whole, demographic studies provide a broad overview of the effects of age on fertility, but they do not permit differentiation among causal factors of infertility. Moreover, these studies are unable to disentangle the effects of coital rate, marriage duration, and the contribution of paternal age to infertility.

Menken et al. used historical data from 10 populations (including one population containing recorded marriages in Canada from 1700 to 1730) to illustrate how fertility declines with age. ¹⁷ After correcting for fertility differences between populations, they reported that fertility compared with the first age category of 20-24 years was reduced on the average by 6 percent in women aged 25-29 years, 14 percent for those aged 30-34 years, and 31 percent for women 35-39 years of age, followed by a sharp decline. Because the contribution from paternal age could not be determined, the infertility was assigned to female aging. ¹⁸ The authors did not discuss whether the fertility data were affected by decreased coital frequency. Cittadini and Palermo, in their 1990 review paper, referred to the same study of 10 populations, but they used the data to support the idea of a sharp decline in fertility after 35 years of age. ¹⁹ Clearly, the interpretation depends on the definition of a "substantial" decline in

fertility. If the effects of male age, marriage duration, and reproductive impairment due to previous births were removed, perhaps a more definitive conclusion could be reached.

Mineau and Trussell mathematically eliminated the effect of male age and marriage duration in an historical Mormon population with the result that little change in female fertility was seen between the end of adolescence and women's mid-thirties. Menken and Larsen located seven populations in which late marriage was common and fertility control was rare, thus removing the drawback to interpretation of reproductive impairment due to marriage duration and decreased coital frequency. They found a risk of childlessness rising from 6 percent in 20-24 year olds to 9 percent in 25-29 year olds, and to 15 percent for women marrying in their early thirties; then risks increased more sharply. Male fertility was found to decline slowly and was still 73 percent of the base rate of their early twenties when they were 50-54 years of age. 22

Henry used a different method to estimate sterility at the different age levels, resulting in higher percentages of sterility at each age level.²³ Although the question was whether or not a substantial decline in fertility occurs at a particular age, the answer was dependent on the particular method used to determine sterility.

Menken et al. reviewed the demographic data in detail, taking into account confounding variables that could bias the data (e.g., high parity, infection, marriage duration, male age, and the definition of infertility as just one year of unprotected intercourse without a conception). They examined modern demographic data with particular regard to the impact of infection on infertility. They concluded that women in monogamous unions face only modest increases in the probability of becoming sterile or infecund before their late thirties. Es

The problem with the demographic data is that they are able to support different specific conclusions, depending on how a "substantial" decline in fertility is defined, and whether authors assume (as Menken et al. did) that historical data give the highest levels of infertility at each age. ²⁶ If that is the case, then the percentages at each age level from historical populations were higher than those in current populations. Such interpretation problems must be taken into consideration when answering the question of whether a substantial decline in fertility occurs at a particular chronological age.

Historical demographic studies cannot provide the medical histories for the participants, and how applicable the results are to modern populations is not clear. It may be that confounding variables such as infection were of great importance in the historical populations. Although modern levels of infection are thought to be high, they could be insignificant compared to historical populations. ²⁷ This would mean that it is not appropriate to extrapolate infertility rates from historical populations.

Olsen reported a strong correlation between maternal age and subfecundity in a modern demographic study of a large population desiring pregnancy, but with sterilized couples excluded from the analysis. He did not find statistical significance in the correlation between paternal age and subfecundity. Unfortunately, the oldest age category used for women was "over 35," and since the rate of decline may have been due primarily to the presence of women over 40 or 45 years of age, the particular age of decline cannot be determined.

The fact that demographic data show the combined effect of intrinsic and extrinsic factors is reemphasized. It is impossible to determine the denominator in the Olsen study as the older women were put into one "over-35" group, i.e., they were not placed into cohorts on an individual year by year basis. The highest level of infertility observed was 22 percent. This result could be explained by reduced coital activity, ²⁹ but the lack of association between subfecundity and the age of the father argues against this.³⁰ Olsen said the association between mother's age and time to pregnancy could have been a purely biological phenomenon or could have reflected an effect of cumulative exposure to fertility-reducing agents.³¹

Demographic data concerning male fecundity are rare, partly due to the difficulty encountered in separating husbands' and wives' ages. To determine if paternal age is a factor separate from maternal age, it is necessary to use a polygamous society with no contraceptive use in which a man marries women of different ages. It is more common to find a young woman married to an older man in polygamous than in monogamous societies, thus eliminating the effect of advanced maternal age on infertility. Such a study was undertaken by Goldman and Montgomery in 1989.32 They looked at subfecundity in five developing countries in which contraception was not used and polygamy was common. They found no increase in infertility attributable to the husband's age. In one country, an effect was observed, but the authors believed that the results were inaccurate because of contraceptive use. Goldman and Montgomery also looked at the effects of maternal age, but again they classified only two groups of women: those 35 and older and those under 35 years of age. The effect of maternal age on infertility was 13 percent in those under 35 and 34 percent in those 35 and older.33

Studies That Focus on Artificially Inseminated Women

The major weakness of demographic studies is that although they show a decline in fertility with increasing age, they cannot accurately assess the particular effects of coital frequency, male age, and the general health of the participants separately from the effect of biological aging. Many authors believe that these problems are satisfactorily addressed by studies that use artificial insemination (AI) to impregnate women whose husbands are azoospermic (not producing sperm). The assumption is that these women are representative of the modern population, and that they are healthy — that their only problem in getting pregnant is the lack of

sperm. The pregnancy rate for each age group in this artificially inseminated category, therefore, is thought to reflect a decline in fertility due to intrinsic factors.

A French study by the Fédération CECOS³⁴ reported the results of AI in 2 193 nulliparous women (who had not borne a child) who had azoospermic husbands. The probability of success after 12 AI cycles with frozen semen was 73 percent and 74 percent for the two groups of women under 31 years of age, 61 percent for women aged 31-35 years, and 54 percent for those women over 35 years of age (the subgroup aged 36-40 years having the same low level of fertility).³⁵ The impact of this study, which got around the problem of coital rate and the influence of male age, was significant, and the findings have been referred to in numerous subsequent articles on aging and infertility. The levels of infertility observed were greater than those seen in the demographic data. This evidence that women over 30 years of age have a decline in their fertility has been widely accepted by physicians.³⁶

John Bongaarts used demographic data to illustrate that natural conception rates were in fact higher than those seen in the AI study.³⁷ He showed that data from the 1976 American National Survey of Family Growth could be modified (by taking into account the percentage of married couples who did not use contraception and did not conceive) to give the following percentages: 6.7 percent of couples aged 20-24 were infertile compared to 10.8 percent for ages 25-29, 16.1 percent for ages 30-34, and 22.9 percent for ages 35-39.³⁸ (He assumed that there is a dramatic increase in infertility after women's late thirties.) Bongaarts referred to a British study by Vessey to show that British women conceive more rapidly and in greater proportions than French women in any of the reported age groups.³⁹ The study used birth rates after contraception was discontinued. However, Hendershot et al. made the point that Bongaarts had failed to exclude women with established fertility. They disagreed with the way Bongaarts interpreted the data and with his method of subject selection.⁴⁰

In more recent research into age and infertility, using Al studies, Virro and Shewchuk reported a 92 percent conception rate in patients completing six cycles of treatment. In patients over 35 years of age, there were significantly lower conception rates and an increased number of cycles to conception. However, the validity of this study was seriously questioned by Stovall and colleagues. Stovall et al. maintained that the studies of Virro and Shewchuk, the Fédération CECOS, and several others were not valid and could not be applied to all women because they did not document whether the women had open tubes, normal mucus characteristics, and regular ovulatory cycles. However, this may not be a valid criticism since this was not known for any of the women, yet a relationship with age was still found.

Studies employing AI found large age-related declines in fertility as early as age 30. However, patient selection in these studies may have been biased, so it is questionable whether their results could be applied to the

modern population at large. The designation for women whose infertility tests indicated no abnormality was "unexplained" infertility. For AI studies to apply to the general population they have to include patients with the "unexplained" designation.

Stovall and co-workers believed that they were working with a sample of women with true unexplained infertility and, therefore, were looking at infertility caused by biological aging. Using frozen semen for AI, they reported that patients 19-34 years of age had an 18.3 percent success rate per treatment month compared to a 13 percent rate for women 35-45 years of age. ⁴³ Unfortunately, their report did not provide data for each of the five age groups between 19 and 45 years of age. Adjacent age groups (such as those 19-24 and 25-29 years of age) were not significantly different. There was a difference of approximately 20 percent in success at 10 cycles, comparing women between 35-39 and 40-45 years of age. ⁴⁴ Additionally, 8 percent of the cycles were performed with fresh semen (not cryopreserved) and these results, though using few patients, showed uniform percentages of conception from 25 to 45 years of age. ⁴⁵ Because the use of fresh semen was not associated with an age-related fertility decline and the relevant statistical analyses were absent, the whole study lost credibility.

Yeh and Seibel's study in 1987, also using fresh semen for AI, resulted in 75 pregnancies for 108 patients. ⁴⁶ Their conclusions were that a higher success rate (and/or smaller number of AI cycles) is positively associated with a patient age of 35 years or less. However, only 10 of the patients were over 35 years of age, with one reported pregnancy. There was no separation of cumulative infertility factors (such as endometriosis or pelvic inflammatory disease [PID]) nor an explanation as to whether medication was required to regulate the cycle. This study does not seem to add greatly to an understanding of the subject.

Studies of the Population with Unexplained Infertility

In addition to general demographic research and studies focussing on AI, another way to get at the question of the contribution of true biological aging to infertility is through direct study of the portion of the population described as having unexplained infertility (i.e., infertility that cannot be explained by current medical knowledge). Among 2 106 couples registered in 12 Canadian infertility clinics, 22.3 percent were classed as having unexplained infertility — a designation applied to infertile couples after both partners have undergone complete infertility workups. If advanced age is the only factor causing the infertility, a larger proportion of older couples would be expected to fall into the unexplained infertility category.⁴⁷

The Canadian study by Collins and Rowe in 1989 looked at the question of infertility and age by studying the percentage of couples diagnosed as having unexplained infertility.⁴⁸ To enter this unique study, all diagnostic tests and case histories had to result in a diagnosis of unexplained infertility in women with regular menstrual cycles, no STD history, and no history of endometriosis. Men required a normal semen

analysis. Collins and Rowe reported that the proportion of female partners who were 30 years of age or older was 8 percent higher than would have been expected from a comparison with the percentages found in other categories of infertility. The 8 percent excess in older couples was in keeping with the notion that delaying first attempts at conception is only one of many factors that influence the prevalence of infertility. They also found that, for infertility in excess of 36 months' duration, whatever the underlying cause for the unexplained infertility, it is clear that it worsens with age, so that age becomes an important independent predictor of likelihood of pregnancy.

Discussion

Menken et al. did not find any evidence from the historical and natural fertility demographic data for a substantial decline in fertility until women reach their late thirties. ⁵² In historical studies, infertility was attributed to women. Léridon, using similar data, suggested that fecundity decreases in women who are older than 30 years of age. ⁵³ Olsen found that 22 percent of the women in his "over-35" age group had to wait longer than a year to achieve pregnancy. ⁵⁴ It is disappointing that so much information was lost because women were arbitrarily grouped into an over-35 category. In addition, instead of offering generalizations such as "a substantial decline in fertility," it would have been more useful if authors had provided percent changes in fertility with respect to the age cohorts and left it for the readers to consider whether differences were substantial.

It is, however, clear from all of the studies that fertility declines with respect to the base fertility rate of women who are between 20 and 24 years old. Because many studies just say that fertility declines, without giving the percent changes, readers cannot decide for themselves whether a decline is substantial in those studies. Researchers often cite the CECOS study, inferring that it has established a substantial fertility decline for women who are older than 30 years of age.

Many reports do not provide a breakdown of results according to specific age group categories, choosing instead to arbitrarily divide the participants into those older than 30 years of age and those younger than 30 (or those over 35 and those under 35). This makes it difficult to compare studies and construct models of relationship of specific age intervals related to fertility decline. This problem, combined with other experimental design features, makes it impossible to determine accurately the specific relationship of yearly age intervals to infertility from either AI studies or the consideration of unexplained infertility, even though it is very clear that fertility declines with age.

More specific recent studies help to pinpoint the underlying relationship between biological aging and infertility. Some data come from the results of trials using assisted human reproduction, gamete intrafallopian transfer (GIFT), and *in vitro* fertilization (IVF). TVF eliminates variability in results attributable to the ability of sperm to

fertilize; GIFT permits multiple eggs to be returned to the uterus. In both methods the hormonal aspects are controlled by medication so that the result should depend only upon the quality of the gametes and the ability of the lining to support implantation. Only animal studies are available to determine independently the role of the hormonal axis. 56

Very few studies have been performed using men. One reason for this may be the assumption that men's fertility declines later in life than women's; however, their reproductive system does not escape aging. One study did find it necessary to include paternal age in its equations to enable prediction of the probability of pregnancy from a particular semen analysis.⁵⁷

The Physiology of Aging of the Reproductive System: Implications for Infertility

Decreased likelihood of having a child occurs as a result of intrinsic factors (i.e., changes in the system due to aging alone), extrinsic factors, and a combination of these agents.

The Effect of True Biological Aging on the Reproductive System of Men and Women

Decrease in reproductive functions due solely to age is referred to as true biological aging. It is manifested in the processes of gamete production, embryo implantation, and ability to carry a pregnancy to term. In essence, true biological aging results in changes in key parts of the reproductive system responsible for producing the gametes, allowing the embryo to implant, and carrying the fetus to term.

A review of the informative article by Gindoff and Jewelewicz⁵⁸ and the work on assisted human reproduction⁵⁹ allows the following age-sensitive components of the reproductive system to be described. The hormonal axis, a set of complicated chemical messages, coordinates the functions of the hypothalamus, the pituitary, and ultimately the testes or ovaries. The gametes (sperm and eggs) themselves are produced within the testes and ovaries. The final two components pertain to women: the lining of the uterus responds to hormones that trigger changes to allow for implantation; a complex group of hormonal and mechanical changes allows the fetus to grow in the womb until it is viable, and also encourages the maternal system to adjust to the changes without causing serious damage or death to either.

The Role of the Hormonal Axis

Because of the hormonal axis' complexity it is probable that the effects of aging act first at this point in the reproductive system. The hypothalamus, the pituitary, the gonads (ovaries or testes), and the hormonal messages that pass between them are involved. It is this system that coordinates and times egg ripening and ovulation in women and sperm

production in men. In women, this precise coordination results in ovulation and menses.

Menopause (the cessation of menses) is said to occur up to 10 years after the age when the potential for childbearing ends. Gindoff and Jewelewicz tried to explain why the ability to bear children ends so far before menopause. In many women under age 45, they said, signs of impending menopause are absent. That is, their cycles are still the same length and still occur regularly; their hormone levels are the same as those found in younger women, and they ovulate during every cycle. The question is, why can these women not have children?

Several reviews suggested there is an increase in luteal-phase defects with age. 62 This means that following ovulation the corpus luteum does not secrete enough progesterone or secrete it for long enough to allow the embryo to embed in the uterus. The pregnancy would therefore be lost with menses. However, recent studies do not support the theory that luteal-

phase defects increase as women age.63

No explanation is known for fertility decline with respect to the hormonal axis until women become perimenopausal, that is, their cycles start to lengthen. In comparison, changes in the rodent hormonal axis actually occur in middle-aged rats before their cycles start to lengthen. A key study from McGill University⁶⁴ showed that both the neuroendocrine portion (hypothalamus and pituitary) of the hormonal axis and the ovaries are responsible for the lengthening of the reproductive cycle in mice, but it is the ovaries themselves that signal the end of cyclicity (menopause) itself. Chronic exposure to the ovarian hormones (felt to play a critical role in cycle lengthening) and the number of eggs left in the ovary control the actual occurrence of menopause. Further evidence from studies on rats showed that the hypothalamus (the pacemaker of the hormonal axis) fails to send the chemical message according to the correct diurnal pattern and, in addition, the pituitary becomes less sensitive to hypothalamic messages. These observations were made in middle-aged rats that still had regular cycles. 65 Studies are not available to confirm that parallel events occur in humans.

Women may experience premature ovarian failure, meaning that they run out of eggs early. Sauer et al. estimated that this occurs in 10 percent of women by age 40.⁶⁶ The clinical sign for this is a rise in the level of follicle-stimulating hormone (FSH). Gindoff and Jewelewicz suggested that women should be checked for rising FSH levels that indicate ovarian failure prior to infertility treatment. Once these levels rise, the reproductive span is over and only by using donated eggs can these women become pregnant.⁶⁷

Little work has been done to document the changes in the hormonal axis that occur with age in men, but a few studies have reported on changes in communication between the pituitary and the testes in men. Of several types of luteinizing hormone (LH), one is found in men with a wide variety of systemic illnesses. Warner and colleagues demonstrated

that older men also reveal an increase in this form of LH, which is correlated with decreased testosterone levels of 25 percent. ⁶⁸ No attempt was made to examine the correlation of these changes with infertility.

The only other study was done by Nieschlag et al. who reported elevated LH and FSH levels in older men but no difference in sperm parameters such as ejaculate volume and sperm morphology between young fathers and grandfathers. ⁶⁹ Sperm motility and seminal fructose levels decreased, but the ability for the sperm to penetrate eggs as determined by the Hamster Zona-Free Ovum Test⁷⁰ did not decline with age. The fertilizing ability of older men was not decreased, they concluded, but there were signs of changes in pituitary and testicular endocrinology.

The Role of the Endometrial Lining

Gindoff and Jewelewicz reported ovulation in most women under 45 years of age; their hormone levels are normal, and they are not yet perimenopausal. The question, therefore, remains, what other facet of the reproductive system could be responsible for the observed age-related decline in fertility?

It is the role of the endometrium to respond to the hormones of the second half (luteal phase) of the reproductive cycle and build up, thereby providing a receptive site for embryos. The second function of the endometrium is to reject abnormally developing embryos.

Comparative studies suggested that the endometrial lining of older animals might not respond normally to hormonal influence. Gosden, working with middle-aged mice, reported that the uterine lining did not respond to hormonal stimulation and that this interfered with the implantation of both normal and abnormal embryos.⁷¹

If the ability of the human endometrial lining to perform its functions changes as women age, then this should be reflected by an increase in the rate of miscarriage in older women. Fertilization occurs but the embryo fails to implant properly and, therefore, is aborted. In fact, the risk of spontaneous first-trimester abortion does increase with maternal age. Because fertility refers to the ability to give birth to a normal child, this means that the older women are less fertile than younger women. The risk of a spontaneous, first-trimester abortion rises from approximately 10 percent for women between 15 and 34 years of age to 17.7 percent for women who are 35-39; to 33.8 percent for those who are 40-43 years old; and to 53.2 percent for women who are 44 years of age or over.⁷²

An indication of the high rate of spontaneous abortion among older women is also obtained from the results of IVF and GIFT programs. Romeu and colleagues from the Jones Institute for Reproductive Medicine, for example, reported a higher total abortion rate (60 percent) for patients 40 years of age or older in comparison with patients 39 years of age or younger⁷³ (including pre-clinical and first-trimester abortions). Previous recurrent spontaneous abortions are associated with subsequent subfertility.⁷⁴

Assisted human reproduction studies in which the hormonal axis is artificially controlled provide evidence about both the competence of the endometrial lining and oocyte quality. One study of IVF indicated that women over 35 years of age have linings less likely to respond to hormones (as determined by endometrial biopsy) than younger women. Half of the patients in this small study had abnormal biopsies, ⁷⁵ which would affect the general applicability of the results. A landmark 1990 study of seven women aged 40-44 years who had premature ovarian failure showed a high likelihood of implantation and pregnancy using donor embryos from younger (under age 35) women. The ongoing pregnancy rates were much better than for women of comparable age (40-44) when their own eggs were used. This finding implies that the uterine lining is capable of responding to hormonal stimulation and providing a suitable environment for implantation. ⁷⁶

After they reviewed the *in vitro* studies, however, Cittadini and Palermo decided that there is a marked drop in fertility after age 36.⁷⁷ They did not consider in their discussion the fact that the lining is capable of responding to hormonal stimulation, thereby providing a suitable environment for the embryo, as is the case for women between 40 and 44 years of age who receive donor embryos from younger women. Cittadini and Palermo were the only specialists to suggest that women over 36 years of age are poor candidates for IVF.

The Role of Germ Cell Quality

If the endometrial lining performs its functions normally, then there must be another cause for the high spontaneous abortion rate found in older women. The ability of two germ cells to combine to produce an embryo does not guarantee that development will proceed normally. If the quality of the germ cells from men and women declines with age, spontaneous miscarriage would be an expected result.

Basically, a decline in quality means that the resulting embryo contains chromosomal abnormalities, which lead either to developmental difficulties great enough to cause spontaneous abortion or to the survival of a fetus with congenital defects. One common example is trisomy 21^{78} (Down syndrome). The vast majority of autosomal trisomies result from primary meiotic non-disjunction in germ cells. This can occur in either the male or female parent and at either meiosis-I or meiosis-II, but the contributor of the extra chromosome is overwhelmingly the female parent.

There is a debate concerning the occurrence of trisomies in eggs of women who are aging.⁸¹ The first major argument, as mentioned above, stipulates a greater likelihood of failure of the chromosomes to separate properly during meiosis in older women. The second theory presupposes a constant rate of trisomy, but a difference in the ability of the uterine lining of older women to expel defective embryos. Thus, a trisomic embryo would not be expelled by an older woman. But there is overwhelming evidence against this uterine "relaxation" theory. Also, the number of

children who have other chromosomal abnormalities besides trisomy and born to older women does not increase. Therefore, the increasing rate of chromosomal defects may arise because of a failure in the mechanics of separating chromosomes in meiosis, or because of the hormonal environment present in older women when their eggs are released. Research indicates a higher proportion of abnormality in the concepti aborted by older women in comparison to younger women.

Eiben and co-workers reported that 50 percent of the 750 spontaneous abortions they examined contained chromosomal abnormalities. ⁸³ Warburton et al. found the frequently reported increase in chromosomal abnormality with increasing maternal age, ⁸⁴ but only for the autosomal trisomies 16, 18, 20, 21, and 22. These trisomies accounted for 62 percent

of the abnormal karyotypes.85

Additional data concerning egg quality have been obtained from IVF and GIFT studies. In both procedures, multiple eggs are induced to mature by using exogenous hormones. One large GIFT study determined that in women over 39 years of age the risk of multiple pregnancy is greatly reduced. But all retrieved eggs (up to 11) have to be used to obtain an acceptable singleton pregnancy rate (20 percent). This could mean one of two things: either that egg quality deteriorates in older women or that the endometrial lining does not function properly. As previously mentioned, preliminary evidence indicates that the fault does not lie with the endometrium.

Padilla and Garcia, in their 1989 study on IVF, found that pregnancy rates were lower for women who were more than 37 years of age. They reported a pregnancy rate of 26 percent per embryo transfer for women who were under 30 years, and 9 percent for women who were over 37. Women who were older than 40 years of age miscarried at a rate of 50 percent, compared to 29 percent for women who were younger than 40. authors believed that the effect of age is more pronounced from 37 years onward.87 Johnston et al., however, reported a conflicting conclusion from their IVF study on the effect of maternal age and the spontaneous miscarriage rate.88 They said that if the cause of the infertility in various couples was separated out, the difference in pregnancy and abortion rates between different age groups would disappear. They found that women diagnosed with unexplained infertility or who had husbands with sperm disorders had a higher rate of abortion and a lower pregnancy rate. This report, however, did not add much to the discussion, because unexplained infertility is the most common diagnosis found in infertile women over 40. (Blocked tubes are the most common diagnosis in women between 36 and 40 years of age.89)

On the other hand, Romeu and colleagues disagreed with Padilla and Garcia — they found that eggs from older women matured properly in response to hormonal treatment. 90 Although the eggs fertilized normally, the spontaneous abortion rate was much higher in women over 40 (60 percent). The ongoing pregnancy rate for these women was 12 percent.

The study did not show any evidence of abnormality in the fetuses of the older women as determined by amniocentesis. Perhaps the results could be explained in relation to research by Day et al. into middle-aged rats. He found that the percentage of eggs that fertilized was the same in older rats as in younger rats, but the embryos displayed a delayed pattern of development and increased morphological abnormalities. The pattern was enhanced in even older animals. The end result was that litter sizes were much smaller. He are the sizes were much smaller.

Felicity Cohen reviewed the contribution of paternal germ cells to inherited genetic abnormalities and reported that 20 percent to 30 percent of the cases of trisomy 21 were of paternal origin. However, Hatch and colleagues, in 1990, examined the chromosomes of spontaneously aborted concepti and found no correlation between paternal age and either trisomy 21 or increased numbers of chromosomally normal aborted embryos. Hen over age 55 also make dramatic contributions to autosomal dominant mutations.

It is difficult to estimate the male contribution to infertility because of the difficulties in converting sperm parameters such as sperm count and morphology into the ability to achieve pregnancy. At the sperm analysis laboratory in Pileastrade, Copenhagen, a semen analysis can be accompanied by a graph that shows the probability of that individual achieving pregnancy as a function of time. In developing the equation to produce this graph, the investigators found that paternal age is an extremely important variable in determining the probability of achieving pregnancy (the other parameters are percentage of morphologically normal spermatozoa and the degree of sperm motility). The effect of age is shown by a smooth decline in the ability to achieve pregnancy from age 20 to age 40. This is despite the fact that measurable semen qualities do not change significantly with age.⁹⁶

Cumulative Infertility Factors in Women and Men

Certain factors such as occupational and environmental hazards, PID, endometriosis, contraceptive use, repeated induced abortion, and smoking have been implicated in damage to the reproductive system. Some of these factors have a greater impact on older women, partly because older women as a group have had more cumulative exposure to these hazards. The status of the reproductive system is determined by the total sum of the effects due to purely biological aging and the effects due to cumulative infertility factors. The effects of cumulative infertility factors will be briefly reviewed.

Endometriosis

Endometriosis is a condition in which retrograde bleeding allows pockets of endometrial cells to migrate and grow in places exterior to the uterus. Moderate and severe forms may cause infertility. The relationship of mild endometriosis to infertility is unclear at present. Cittadini and Palermo cited endometriosis as one of the factors that can

damage the female reproductive tract and cause infertility.⁹⁹ It can cause blockage of the fallopian tubes. Its progression (it worsens with age) can be halted, at least partially, through repeated surgery and hormonal treatments.¹⁰⁰ One study, that of Houston in 1984, revealed a positive correlation between increasing age and the risk of acquiring endometriosis.¹⁰¹

Sexually Transmitted Diseases and Pelvic Inflammatory Disease

Another condition that damages the female reproductive tract is PID. The debate that exists is not over whether this condition causes infertility, but how prevalent it is in the population and the extent of its impact. Menken et al. thought it did not add a significant amount to age-specific infertility. Gindoff and Jewelewicz believed women with this disorder belonged to a high-risk subgroup, which they did not think was numerically important in deciding when age becomes a factor in infertility. Tulandi, a Canadian physician, disagreed because his research showed that tubal factor is the single most common reason for infertility in women aged 36-40 years. Though the results were suggestive, a larger group of women needs to be considered, as the study was very small.

One way to acquire blocked fallopian tubes is through an infection that leads to PID. A study from San Francisco reported the risk of developing PID for women between the ages of 15 and 19 years. The observed rate was 1 in 8, but if the current trend continues 50 percent of women who were 15 years old in 1970 in that population will have had at

least one episode of PID by the year 2000. 106

The serious nature of this problem was revealed in Weström's 1990 study of the sequelae to episodes of PID. ¹⁰⁷ He found the prevalence of PID (acute salpingitis) to be 10 to 13 per 1 000 (sexually active women) and strongly correlated with the prevalence of STDs, legal abortion, and use of an intrauterine contraceptive device (IUD). Infertility ranged between 5.8 percent and 60 percent, depending on the number of episodes and also the woman's age. An examination of 400 women 10 years after treatment showed that 12.8 percent were sterile after one infection and 35.5 percent after two infections (and the figures were even higher with increasing age). Infecundity from a single episode increased with both age and the severity of the infection, ¹⁰⁸ and there was a tenfold risk of having an ectopic pregnancy following the PID episode. ¹⁰⁹ Uterine pregnancy rates after one ectopic pregnancy where PID is implicated are low (in the Nagamani et al. study, 19 percent). ¹¹⁰ The percentages improve only for women who are under 25 years of age at the time of the ectopic pregnancy.

Eschenbach estimated that of sexually active women, 1 percent would develop PID; 10 percent of these would experience infertility, 5 percent would have an ectopic pregnancy, 15 percent would experience chronic pain, and 25 percent would be reinfected. His list of causal organisms included: *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, genital mycoplasma, and a wide variety of bacterial diseases.¹¹¹ In many countries

there has been a noticeable shift from gonococcal to chlamydial infection. Since chlamydia in women is often asymptomatic, a PID resulting from a chlamydial infection could go undiagnosed until infertility workups are

done or an ectopic pregnancy is diagnosed.

Ectopic pregnancy is on the increase in most countries. ¹¹² Eschenbach estimated that 5 percent of women who develop PID will later have an ectopic pregnancy. Ectopic pregnancy, which is a life-threatening condition, can result when fibrous adhesions occur within the fallopian tubes as the result of chronic PID. ¹¹³ In a Melbourne study in 1981, for example, 35 percent of women operated on for ectopic pregnancy had chronic PID. ¹¹⁴ Although increasing age was a significant risk factor for ectopic pregnancy, it was confounded by the presence of diagnosed PID.

Very similar results were found in a Finnish study by Makinen et al. that proved that their country's tremendous increase in ectopic pregnancy rate between 1966 and 1985 could only be explained by adding together the risks of age, past pelvic operation, previous PID, antecedent legal abortion,

and concurrent use of an IUD.115

A Finnish follow-up study of 110 women indicated that 65 percent of women seeking to have a child after an ectopic pregnancy did become pregnant again: the recurrence rate of ectopic pregnancy was 20 percent and infertility 15 percent. The result was better for patients who were under 30 years of age at the time of the ectopic pregnancy and who had been using an IUD for contraception when the ectopic pregnancy occurred. However, Nagamani et al. showed that the uterine pregnancy rate after an ectopic pregnancy was poor for women who had a previous history of PID (19 percent); these women had a high incidence of recurrent ectopic pregnancy (27 percent). The pregnancy rate was higher only in women who were under age 25 at the time of the ectopic pregnancy.

Exposure to Drugs, Chemicals, and Occupational Hazards

In addition to infection, and various other conditions that affect the reproductive tract, men and women may be exposed in places of work or in their general environment to substances that decrease fertility. As humans age, they have a longer opportunity for potential exposures to hazards that impair fertility. Cohen and Narod agreed that it is extremely difficult to perform studies that will give definitive answers as to whether a chemical hazard actually affects human reproduction. The question of whether the reproductive systems of older men and women are more sensitive to a hazard than the systems of younger women and men is even more difficult to approach. Cohen and Narod et al., in their respective review papers, reported that several criteria have to be met in studies that correlate chemical exposure and female infertility. It is necessary that the chemical not be transported with the semen; that it does not linger into pregnancy; and that the fetus is not exposed in utero. 118 Because all of these conditions have to be satisfied, the number of studies that can test for a relationship between an environmental hazard and female infertility is limited.

Some studies exist that revealed a link between impaired fertility and exposure to an occupational hazard. For example, that the rate of miscarriage is increased in women exposed to anaesthetic gas is well documented. 119 Women exposed to anti-convulsants are at a higher risk of having children with birth defects. Primary infertility may result from the use of various individual anti-neoplastic agents (such as cyclophosphamide, chlorambucil, busulfan, and methotrexate) and combinations of these chemotherapeutic drugs, glucocorticosteroids, and hormonal steroids (diethylstilbestrol, medroxyprogesterone acetate, estrogen, and the constituents of oral contraceptives). There is also an effect due to the antibiotics sulfasalazine and co-trimoxazole, thyroid supplements, spironolactone, cimetidine, colchicine, marijuana, opiates, and neuroleptic agents — described in a 1984 study by Buchanan and Davis. 120 A small study by Wilcox et al. showed that women who consumed more than the equivalent of one cup of coffee per day were half as likely to become pregnant per cycle as women who drank less; a dose-response effect was present. 121 However, in a large Danish study of 10 886 subjects, Olsen found no correlation between the consumption of caffeinated beverages and increased infertility in non-smokers. There was a significant increase in subfecundity found in smokers who also drank eight cups of coffee or the equivalent in tea daily. 122 (Subfecundity in this study was defined as a waiting time of one year or more from cessation of contraception to achievement of pregnancy.)

The risk of spontaneous abortion can be increased with exposure to solder fumes. Diagnostic radiation has a strong effect on the rate of miscarriage and fertility problems and appears to combine with the use of oral contraceptives to increase post-pill amenorrhoea. There is overwhelming evidence to suggest that there is not an increased odds ratio for miscarriage obtained from exposure to video display terminals. One such study of over 200 000 subjects was reported from Norway and found no such correlation. A more recent U.S. study found no increase in the risk of spontaneous abortion associated with the occupational use of video display terminals, though the upper confidence limit on the odds ratio (1.39) could not exclude a small or moderate positive association. Suggestive results were obtained from another study concerning exposure to water contaminated with trichloroethene.

It is easier to make the connection between exposure to toxins and infertility in men because the effects during gestation can be excluded. 128 There have been, however, no studies that report on the sensitivity of the older male reproductive system to environmental damage compared to the systems of younger men. Again, there are two questions: Is the older male reproductive system more sensitive to damage than the younger male system? Is the older male reproductive system at risk because of the

cumulative effect of exposure over time to hazards? Zenick et al. reported that there was little definite evidence regarding the result of exposure to various chemical and physical agents because of problems matching controls and dosage, the duration or timing of the exposure, and synergism with other agents that were present at the same time. Yery few chemicals or hazards have actually been studied, and, as exposure may mean cumulative damage to the reproductive system, it is apparent that very little is known about the effect of exposure on the male reproductive system.

Sperm must be continually produced and millions of sperm must mature properly. If there is damage to the spermatocytes¹³⁰ themselves then no further sperm can develop. One of the most serious results in terms of male infertility arose from a study concerning the soil fumigant (1,2-dibromo-3-chloropropane [DBCP]), which revealed that reproductive impairment could occur without any other signs of clinical toxicity. This is disturbing in that exposure to thousands of substances that have not been tested and that have the potential to cause reproductive impairment occurs. There may be no clinical warning signs to alert men that their fertility is at risk.

The adverse effects of lead on the reproductive systems of men and women have been well documented. Exposure to lead can affect the reproductive system prior to conception by damaging germ cells, altering menstrual and ovarian cycles, reducing fertility in women, decreasing libido and fertility in men, and altering spermatogenesis. During pregnancy, exposure to lead is known to cause spontaneous abortion, stillbirth, and damage to the fetus. After birth, children of lead-exposed parents may exhibit birth defects and neurological damage, and the chance of death during the first year of life increases. ¹³³

The effect of alcohol on fertility is currently under investigation and as yet there is no definite conclusion regarding alcohol and infertility. Morphia is known to lower testosterone levels. Anti-hypertensive medicine, cancer therapy, vinblastine, and DBCP decrease fertility and cause increased spontaneous abortions. Carbon disulphide (used in dry cleaning) increases the percentage of semen abnormalities and the spontaneous abortion rate. Alkylating agents cause low sperm counts, and infertility is increased by exposure to Agent Orange, radiotherapy, and chemotherapy. Paternal exposure to anaesthetic gases can also cause a higher rate of miscarriage. 135

A few studies have connected occupation and sperm count. Again, these studies were very difficult to perform because of the difficulty in getting adequate controls and estimating dosages. It is unlikely that the individuals involved in these studies voluntarily exposed themselves to hazards. Therefore, as no systematic record was being kept of their exposure, it was very difficult both to determine how much exposure there was and to have matched controls in terms of health, age, and occupation. A study by Whorton and Meyer on sperm counts for workers at 14 different workplaces showed that no increase in oligospermia (less than 20 million

sperm per millilitre) was found in comparison with a control group. ¹³⁶ Henderson et al., however, found an association between infertility (indicated by sperm count) and male occupation: sperm concentrations were significantly different and found to be highest in administrative and professional groups and lowest in farming and transport groups. Reported exposure to heat and chemicals was also significantly different between occupations, and may have contributed to the lower sperm concentrations. There is an urgent need for more data. ¹³⁷ In fact, the effect of dropping the sperm count, as long as it remains above the World Health Organization's definition of oligospermia, is unknown. But the Pileastrade laboratory found that sperm motility and morphology were important in predicting pregnancy outcomes rather than sperm count per se.

Smoking

Studies done on the effects of smoking on subfecundity clearly state that smoking in either parent causes conception delay. The longer the delay, the more significant the effect of even light smoking. For example, in one study of 678 people, 138 38 percent of non-smokers conceived in their first cycle compared to 28 percent of smokers. Smokers were 3.4 times more likely to have taken longer than a year to conceive than non-smokers. After adjusting for potential confounding variables, the fertility of smokers was estimated to be 72 percent of the fertility of non-smokers. Heavy smokers were observed to have lower fertility than light smokers (57 percent and 75 percent).

Suonio et al. showed that the reproductive systems of men and women older than 35 years of age are more sensitive to the effect of smoke than the reproductive systems of younger people. The effect appears to be stronger in women, but for both sexes the end result is an increased risk of infertility in the form of conception delay in older people who smoke, compared to younger people who smoke.

Contraceptives and Induced Abortion

The probability of infection after a first-trimester induced abortion is documented to be low. However, every time the procedure is repeated, so is the risk of getting PID; thus, Huggins and Cullins believed that the risk for developing pelvic infection is a multiple of the number of abortions. As women get older the probability that they have used contraceptives or undergone an induced abortion increases.

In young women, the use of oral contraceptives does not appear to be related to long-term infertility. Post-pill amenorrhoea greater than six months is found in only 1 percent of these women, and their fertility rates are normal within a year. For older women who have used oral contraceptives for several years, the effect is greater and the period of time without cyclicity is longer. Greenfeld and DeCherney, however, disagreed with this conclusion. They believed the effect on infertility is due to environmental factors or maternal age rather than contraceptive use. 142

The presence of an IUD increases the risk of developing PID, particularly in the months following insertion, but several recent articles have concluded that the safety of newer devices, such as the copper-releasing IUD, is greater than that of the older ones. 143

Pregnancy Outcome for Older Women

Is there an effect due to advancing age on the ability to successfully carry a child when success is measured by fetal outcome and maternal survival? Two recent studies can be used to look at this question. A British study in 1988 found that there was four times the incidence of pre-term births in "elderly primigravidae" (women over 35), five times the rate of Caesarian section, significantly increased rates of chronic hypertension and fibroids, and a tendency toward the more serious problems of pre-eclampsia and perinatal death (outcomes of elderly primigravidae were compared to those of 20-24 year olds). 144 However, this small study must be examined in comparison to a large U.S. study that looked at the difference in pregnancy outcome for women aged 20-34 and those who were older than 35. 145 Peripartum complications were no more frequent in the older than 35 group, though Caesarian sections were more common. The rates of adverse fetal outcomes for the younger women and the older women were indistinguishable. In fact, there were actually fewer perinatal deaths in the older group and fewer babies with congenital defects, as these women had access to amniocentesis and the choice of termination of pregnancy of fetuses with documented chromosomal abnormalities.

There are very few adequate, population-based studies that examine the relationship of maternal age to likelihood of congenital defects that are not of chromosomal origin nor hereditary. This is, perhaps, because these studies require data on the ages of the women giving birth, assessment of the babies for defects at later ages as well as at birth, the results of amniocentesis, and the etiology, if known, of congenital defects that occur. However, British Columbia has a centralized prenatal diagnosis program that collects accurate information on maternal ages and birth defects for all births in the province. The findings from a large population-based analysis of almost 27 000 children were that, excluding children with chromosomal anomalies and those with defects of known etiology, there was no association between the incidence of birth defects of unknown etiology and advanced maternal age. Two U.S. studies concurred with this finding, though they did not look at specific categories of birth defects. 147

With regard to older fathers, all that can be said is that they have a somewhat higher risk of having babies with serious defects, when all types of defects are combined. Friedman estimated the risk of fathers 40 years of age or over of having babies with defects caused by fresh dominant mutations to be 3 to 5 per 1 000 births. 149

An Australian study also reported optimistic findings concerning age, 150 and Gindoff and Jewelewicz, in their review paper, concurred that

older women, apart from miscarriage and chronic anomalies, do not have pregnancy outcomes very different from those of younger women. 151

Findings

Infertility is a difficult topic to research because it means different things to different authors. Many investigators restrict the term "infertility" to mean exclusively the ability to conceive, or at best the ability to conceive and to avoid first-trimester miscarriages. To a couple who wants a child this definition is not adequate. Furthermore, because of the different interpretations of infertility, some research groups do not concern themselves with the findings of other groups. For example, groups involved in assisted human reproduction consider their own findings in determining when age affects infertility — the same applies to groups using AI. Pregnancy outcome and non-chromosomal congenital defects as outcomes when trying to establish the relationship of age to infertility tend to be neglected. However, two major themes emerge: attempts have been made to elucidate the relationship between age and infertility, including an examination of the physiological basis; and researchers have also considered the impact of cumulative factors on age-related fertility decline.

Demographic studies found a substantial decline in fertility (meaning a delay in conception) for women who had reached their late thirties. Studies of AI and unexplained infertility have been concerned primarily with showing whether or not a substantial decline occurs after age 30. Various demographic studies and AI studies show that from one-quarter to one-half of women in their late thirties are infertile. However, studies using AI had serious problems regarding patient selection and patient assessments and thus were limited in their contribution to an understanding of when a substantial decline in fertility occurs.

Spontaneous abortion is the biggest hazard for women over 40, except for the very small number who have received eggs donated from younger women. Egg quality appears to decline rapidly after age 40; the incidence of trisomy rises from age 30 onward, and even more rapidly after age 40. However, increased maternal age is not associated with higher rates for other forms of chromosomal abnormality, or with congenital defects of non-chromosomal etiology. The paternal contribution to birth defects, via germ cell deterioration (sperm aging), appears to be limited to a contribution to Down syndrome and an increased incidence of autosomal dominant mutations in older men (possibly over 50 years of age).

Little information was located on the role of acquired infertility factors on age-related fertility. Many potentially damaging substances are found in the environment. The arbitrary grouping of people, particularly women, into above or below 35 years of age has hindered the determination of the exact ages when extrinsic infertility factors may become important

determinants of fertility decline. There are a few well-documented hazards, such as the effect of smoking on both male and female fertility, and the damage done by even a single episode of PID.

Little work has been done regarding the paternal role in infertility. However, one author has suggested, on the basis of paternal contributions to birth defects, that families should be completed before men reach 40 years of age. 152

In summary, it is quite clear that, for women, the time needed to conceive increases during the thirties. The rate of spontaneous abortion rapidly increases after age 40, due to an increase in abnormal conception. The role of advanced paternal age is unclear, but from the little work that has been done, it appears to be less important than advanced maternal age.

Notes

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- 2. Canada, Statistics Canada, *Births 1990*, Health Reports Suppl. 14, Cat. 82-003 (Ottawa: Minister of Supply and Services Canada, 1992).
- 3. The concept of natural fertility was first developed by L. Henry in 1961. In a recent study, Judy C. Felt and colleagues studied Old Colony Mennonites in Mexico, who had migrated from Manitoba in the 1920s. This population has age-specific marital fertility rates and birth intervals that closely resemble those of the Hutterites. Both the Hutterites and the Old Colony Mennonites in Mexico appear to demonstrate natural fertility (i.e., they use no form of artificial birth control and apparently do not attempt to limit family size). J.C. Felt et al., "High Fertility of Old Colony Mennonites in Mexico," Human Biology 62 (1990): 689-700.
- 4. The term "age-specific infertility" refers to observed decline in fertility with respect to age of cohort. J. Menken, J. Trussell, and U. Larsen, "Age and Infertility," *Science* 233 (1986): 1389-94.
- 5. Normal biological aging refers to inherent age-related biologic factors. There are several different expressions used by authors to separate out the deterioration that occurs in the reproductive system strictly due to the aging process from a deterioration caused by exposure to various hazards in the environment. One obvious example is the sequelae on the functioning of the female reproductive tract after an episode of PID: "normal biological aging" from Menken et al., "Age and Infertility," 1394; "inherent age-related biologic factors" from P.R. Gindoff and R. Jewelewicz, "Reproductive Potential in the Older Woman," Fertility and Sterility 46 (1986), 990.
- 6. Menken et al., "Age and Infertility." The question surrounding the use of the various terms is outlined in the introduction of this demographic review paper.
- 7. The medical definition of infertility is the inability of a couple to conceive after one year of unprotected intercourse. Menken et al., "Age and Infertility."

- 8. J. Olsen, "Subfecundity According to the Age of the Mother and the Father," Danish Medical Bulletin 37 (1990): 281-82.
- 9. It would be preferable to use the biological age of an individual rather than the chronological age in discussing the role of aging in infertility. For example, in women the biological age could reflect a woman's proximity to menopause and whether her system has aged because of extrinsic factors. Unfortunately, we do not currently have an accurate method of ascertaining a person's biological age and, accordingly, people are classified within studies by their chronological age.
- 10. MEDLINE is the largest and most frequently used data base and contains references to recent biomedical journal articles. In MEDLINE and its backfiles, which cover the literature from 1966, there are approximately 6 million records. The MEDLINE data base contains citations from about 3 500 biomedical journals published in the United States and 70 other countries. It corresponds to the printed tools *Index Medicus*, *Index to Dental Literature*, and *International Nursing Index*.
- 11. The Medical Subject Heading (MeSH) list is a comprehensive list of key words used by authors to characterize their work. The following headings were searched: male and female aging and fertility, infertility; infertility and various factors; spontaneous abortion; congenital defects; and the components of the reproductive system (with aging).
- 12. Menken et al., "Age and Infertility"; J. Yeh and M.M. Seibel, "Artificial Insemination with Donor Sperm: A Review of 108 Patients," *Obstetrics and Gynecology* 70 (1987): 313-16; Fédération CECOS, D.B. Schwartz, and M.J. Mayaux, "Female Fecundity as a Function of Age," *New England Journal of Medicine* 306 (1982): 404-406; J.A. Collins and T.C. Rowe, "Age of the Female Partner Is a Prognostic Factor in Prolonged Unexplained Infertility: A Multicenter Study," *Fertility and Sterility* 52 (1989): 15-20.
- 13. D.W. Stovall et al., "The Effect of Age on Female Fecundity," *Obstetrics and Gynecology* 77 (1991): 33-36; Menken et al., "Age and Infertility." An infertility workup performs two functions with regard to a study connecting aging and infertility. It eliminates from the study individuals suffering from identifiable acquired infertility factors such as endometriosis. It can be used to determine if a sample population is healthy and, therefore, representative of the population at large.
- 14. E. Cittadini and R. Palermo, "Infertility in Advanced Reproductive Age: Results of In Vitro Fertilization and Embryo Transfer According to the Woman's Age," Acta Europaea Fertilitatis 20 (1989): 285-97; W.I. Johnston et al., "Patient Selection for In Vitro Fertilization: Physical and Psychological Aspects," Annals of the New York Academy of Sciences 442 (1985): 490-503; B. Eiben et al., "Cytogenetic Analysis of 750 Spontaneous Abortions with the Direct-Preparation Method of Chorionic Villi and Its Implications for Studying Genetic Causes of Pregnancy Wastage," American Journal of Human Genetics 47 (1990): 656-63; M. Hatch et al., "Paternal Age and Trisomy Among Spontaneous Abortions," Human Genetics 85 (1990): 355-61; F.L. Cohen, "Paternal Contributions to Birth Defects," Nursing Clinics of North America 21 (1)(1986): 49-64; D.S. Seidman, P. Ever-Hadani, and R. Gale, "Effect of Maternal Smoking and Age on Congenital Anomalies," Obstetrics and Gynecology 76 (1990): 1046-50.

- 15. C. Tietze, "Reproductive Span and Rate of Reproduction Among Hutterite Women," Fertility and Sterility 8 (1957), 89; Felt et al., "High Fertility of Old Colony Mennonites." Populations that are said to have natural fertility are characterized by the absence of birth control usage and voluntary sterilization. It is felt that a population that has the average age of last birth in the thirties is exhibiting birth control use and not natural fertility.
- 16. N. Goldman and M. Montgomery, "Fecundability and Husband's Age," Social Biology 36 (1989): 146-66.
- 17. Menken et al., "Age and Infertility," 1389.
- 18. Ibid.
- 19. Cittadini and Palermo, "Infertility in Advanced Reproductive Age."
- 20. G.P. Mineau and J. Trussell, "A Specification of Marital Fertility by Parent's Age, Age at Marriage and Marital Duration," *Demography* 19 (1982), 335.
- 21. J. Menken and U. Larsen, "Fertility Rates and Aging," in *Aging, Reproduction* and the Climacteric, ed. L. Mastroianni and A.C. Paulsen (New York: Plenum Press, 1986), 147-66.
- 22. Mineau and Trussell, "Marital Fertility by Parent's Age," 335.
- 23. L. Henry, "French Statistical Research in Natural Fertility," in *Public Health and Population Change: Current Research Issues*, ed. M.C. Sheps and J.C. Ridley (Pittsburgh: University of Pittsburgh Press, 1965), 333-50.
- 24. Menken et al., "Age and Infertility." The arbitrary definition of infertility is: the inability to conceive after one year of unprotected intercourse. Menken and co-workers review historical data from rural English parishes that show that more than 23 percent of couples aged 20-24 did not have a child within two years, but only 4.6 percent never had a child.
- 25. Ibid., 1389.
- 26. Cittadini and Palermo, "Infertility in Advanced Reproductive Age"; Gindoff and Jewelewicz, "Reproductive Potential." Cittadini and Palermo cite the data by Menken and Larsen as supporting evidence for the position that a substantial increase in infertility occurs after age 35. Gindoff and Jewelewicz use historic demographic data to show that fertility is decreased in women older than 30. But these authors do not explain how they reached these conclusions or what their definition was for a substantial decline in fertility. It is not clear that they fully reviewed the demographic data and its associated confounding variables (as Menken et al. did).
- 27. Menken et al., "Age and Infertility."
- 28. Olsen, "Subfecundity According to Age."
- 29. W.H. James, "The Causes of the Decline of Fecundability with Age," Social Biology 26 (1979), 330.
- 30. Olsen, "Subfecundity According to Age," 282.
- 31. Ibid.
- 32. Goldman and Montgomery, "Fecundability and Husband's Age." This study was successful in that it removed the effect of female age. However, because the

cottal frequency could vary among wives, this had to be accounted for mathematically.

- 33. Ibid., 163.
- 34. Fédération CECOS et al., "Fecundity as a Function of Age."
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- 36. Gindoff and Jewelewicz, "Reproductive Potential"; Menken et al., "Age and Infertility"; Cittadini and Palermo, "Infertility in Advanced Reproductive Age."
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- 38. Ibid., 77.
- 39. Ibid.
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- 42. Stovall et al., "Effect of Age on Female Fecundity," 33.
- 43. Ibid.
- 44. Ibid., 36.
- 45. Ibid., 33.
- 46. Yeh and Seibel, "Artificial Insemination with Donor Sperm," 313.
- 47. Collins and Rowe, "Age of the Female Partner," 15. The percentage of older couples with other reasons for their infertility, such as endometriosis or a failure to ovulate, is compared to the percentage found in the unexplained infertility group.
- 48. Collins and Rowe, "Age of the Female Partner."
- 49. Ibid., 15.
- 50. Ibid., 19.
- 51. Ibid.
- 52. Menken et al., "Age and Infertility."
- 53. H. Léridon, Human Fertility: The Basic Components (Chicago: University of Chicago Press, 1977), 107.
- 54. Olsen, "Subfecundity According to Age."
- 55. Cittadini and Palermo, "Infertility in Advanced Reproductive Age"; Johnston et al., "Selection for In Vitro Fertilization"; I. Craft et al., "Analysis of 1071 GIFT Procedures The Case for a Flexible Approach to Treatment," *Lancet* (14 May 1988): 1094-98.
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- 45-57; P.M. Wise et al., "Contribution of Changing Rhythmicity of Hypothalamic Neurotransmitter Function to Female Reproductive Aging," *Annals of the New York Academy of Sciences* 592 (1990): 31-43; discussion 44-51.
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- 59. Craft et al., "1071 GIFT Procedures"; Cittadini and Palermo, "Infertility in Advanced Reproductive Age"; A. Romeu et al., "Results of In Vitro Fertilization Attempts in Women 40 Years of Age and Older: The Norfolk Experience," Fertility and Sterility 47 (1987): 130-36; M.V. Sauer, R.J. Paulson, and R.A. Lobo, "A Preliminary Report on Oocyte Donation Extending Reproductive Potential to Women over 40," New England Journal of Medicine 323 (1990): 1157-60.
- 60. Gindoff and Jewelewicz, "Reproductive Potential."
- 61. Ibid.
- 62. Ibid.; D.A. Greenfeld and A.H. DeCherney, "Age and Fertility," *Current Therapy of Infertility* 3 (1988): 144-46.
- 63. M.G. Metcalf and J.H. Livesey, "Pregnanediol Excretion in Fertile Women: Age-Related Changes," *Journal of Endocrinology* 119 (1988): 153-57; T.C. Li et al., "A Comparison of Some Clinical and Endocrinological Features Between Cycles with Normal and Defective Luteal Phases in Women with Unexplained Infertility," *Human Reproduction* 5 (1990): 805-810. Metcalf and Livesey collected urine samples from 100 women between the ages of 20 and 48, 96.8 percent of whom had regular cycles. They found there was no age-related change during the luteal phase. This was confirmed by Li et al.
- 64. Nelson and Felicio, "Reproductive Aging in Mice."
- 65. Wise et al., "Changing Rhythmicity of Hypothalamic Neurotransmitter."
- 66. Sauer et al., "Preliminary Report on Oocyte Donation."
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- 68. B.A. Warner, M.L. Dufau, and R.J. Santen, "Effects of Aging and Illness on the Pituitary Testicular Axis in Men: Qualitative as well as Quantitative Changes in Luteinizing Hormone," *Journal of Clinical Endocrinology and Metabolism* 60 (1985): 263-68.
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- 72. D. Warburton et al., "Cytogenetic Abnormalities in Spontaneous Abortions of Recognized Conceptions," in *Perinatal Genetics: Diagnosis and Treatment*, ed. I.H. Porter, N.H. Hatcher, and A.M. Willey (New York: Academic Press, 1986), 133.
- 73. Romeu et al., "Results of In Vitro Fertilization Attempts."

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- 77. Cittadini and Palermo, "Infertility in Advanced Reproductive Age."
- 78. Trisomy means that instead of an embryo receiving one copy of each chromosome from each parent, a mistake has been made resulting in three copies of a particular chromosome in the offspring. The extra chromosome can be from the man or woman. Small chromosomes such as number 21 are particularly at risk of being transferred to the offspring in this fashion.
- 79. Primary oocytes which are 2n and contain 46 chromosomes must undergo two divisions to result in eggs that are haploid (containing 23 chromosomes). This process is called meiosis. The two divisions are meiosis-I and meiosis-II respectively. In oogenesis the primary oocytes enter the first meiotic division, but do not finish it. (They remain at this stage until that particular egg undergoes ovulation.) Primary oocytes can remain frozen at this stage for months or for as long as 50 years. It is well known that older women are more likely than younger women to give birth to children with chromosomal defects of the trisomy type, meaning that there is an extra copy of an autosomal chromosome in the egg. The reason may be that the oocytes have remained in the first meiotic division I or meiosis division II.

Spermatogenesis involves the same two divisions, but without the pause between them. S.B. Oppenheimer and G. Lefevre, Jr., *Introduction to Embryonic Development*, 3d ed. (Boston: Allyn and Bacon, 1989).

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- 83. Eiben et al., "Cytogenetic Analysis of 750 Spontaneous Abortions."
- 84. Warburton et al., "Cytogenetic Abnormalities in Spontaneous Abortions," 133. Only a small number of trisomies survive for an entire gestation to give rise to conditions such as Down syndrome.
- 85. The karyotype of an individual is the chromosomal pattern (i.e., the size, shape, and number of chromosomes in their cells). Oppenheimer and Lefevre, *Introduction to Embryonic Development*; Eiben et al., "Cytogenetic Analysis of 750 Spontaneous Abortions," 656.
- 86. Craft et al., "1071 GIFT Procedures."
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Effects of Licit and Illicit Drugs, Alcohol, Caffeine, and Nicotine on Infertility

Hélène Boyer



Executive Summary

This paper is a review of the literature studying the effects of the use of licit and illicit drugs on fertility. The paper is divided into four sections, corresponding to four categories of licit and illicit drugs: drugs affecting the central nervous system (CNS), such as morphine, cocaine, narcotics, and barbiturates; drugs affecting the autonomic nervous system — that is, anti-hypertensive drugs and medication prescribed for gastrointestinal illnesses; chemotherapeutic drugs (this section includes the effects of irradiation); and alcohol, caffeine, and nicotine (cigarettes).

For drugs affecting the CNS, the adverse side-effects depend on the quantity, frequency, and duration of intake, as well as on the person's age. Frequent use during adolescence increases the risk of infertility, and use during pregnancy increases the probability of spontaneous abortion.

On the whole, marijuana seems to have little effect on fertility. The use of cocaine for fairly long periods (two to five years) seems to produce a decrease in sperm production, reduced motility, and an increase in rates of infertility, in direct relation to the duration of use.

Cocaine addiction is associated with a very high rate of spontaneous abortion in pregnant females. The use of morphine and heroin seems to cause infertility, mainly by inhibiting erection in males and preventing ovulation in females. Barbiturates cause menstrual problems. Anti-depressants and anti-psychotic agents appear to produce problems with erection or ejaculation in males, and problems with menstruation in females.

Anti-hypertensive drugs may cause difficulties in achieving orgasm, loss of libido, and problems with achieving erection in males. The drug cimetidine, prescribed for chronic hepatitis, causes sexual dysfunction and reduced sperm production.

Chemotherapeutic drugs and irradiation may produce amenorrhoea in females, which may be reversible, depending on the patient's age. In males, chemotherapy produces azoospermia, which is not permanent but may last up to five years after the end of treatment.

Alcohol may cause infertility in males by attacking the testicles and their functions, as well as by causing impotence. In females, it causes an irregular menstrual cycle. In pregnant females, it doubles the rate of spontaneous abortion and may cause fetal alcohol syndrome.

Caffeine is known to spread rapidly throughout the human body tissues. The rates of infertility in females have been associated with increasing rates in the daily intake of caffeine. In pregnant females, high caffeine consumption may increase the risk of spontaneous abortion and produce early labour contractions and low fetal weight.

Studies of the effects of cigarettes on males show conflicting results. They seem to have established, however, that simultaneous intake of coffee and nicotine reduces the motility and the survival rate of spermatozoa. In females, the effects of cigarettes are evident, and they include menstrual problems and early menopause. The effects of nicotine on pregnancy are increased risk of spontaneous abortion, premature birth, low birthweight, perinatal mortality, and sudden infant death syndrome. Cigarettes also increase the rate of infertility.

Introduction

Before discussing the central theme of this survey of the literature, we must first define the term "infertility." It designates a failure to conceive after one year of sexual relations without contraception. According to Alexander (1982) and Berkowitz (1986), this definition is consistent with most of the studies, which show that approximately 90 percent of couples succeed in conceiving within a period of 12 months. Other researchers, however, state that this period is too short and suggest instead that infertility should be diagnosed only after a period of two years (*Dictionnaire de médecine Flammarion* 1982).

In order to study infertility in a couple, both spouses must be examined. Infertility in men results from the inability of their sperm to fertilize an ovum. Each of the following may be associated with male infertility: insufficient or abnormal spermatogenesis; sperm abnormalities, such as low sperm motility or asthenospermia, excessively high or low sperm volume, abnormal production (frequently associated with varicocele,

emotional stress, and/or exposure to physical or chemical agents), low sperm count or total absence of sperm (oligospermia or even azoospermia), and morphological abnormalities; cryptorchidism, which is an abnormal functioning of the testicle often attributed to orchitis, hormonal disorders, or genetic or congenital disorders of the male reproductive system; and, lastly, obstructions in the tubes of the reproductive system. Sexually transmitted diseases (STDs) and infections are the main causes of such obstructions.

In women, infertility may be associated with problems in ovulation, uterine-vaginal abnormalities, blocked tubes in the reproductive system, or endometriosis. Ovulation disorders include a complete absence of ovulation (anovulation) and ovulatory insufficiency at regular intervals. According to Crooks and Baur (1990), such disorders are a frequent problem in women. The following factors may be associated with ovulation disorders: advanced age of the woman, hormonal imbalance, nutritional and vitamin deficiency, emotional stress, excessive physical exercise, significant weight loss, exposure to certain physical and chemical agents, and, lastly, polycystic ovarian disease. Uterine-vaginal abnormalities may be attributed to gonadal dysgenesis, to cervicitis, or to abnormalities in the cervical mucus. Lastly, obstruction of or infections in the tubes of the reproductive system may be associated with STDs or with other infections.

A distinction is drawn between two general types of infertility. Primary infertility means conception has never occurred. Secondary infertility refers to the couple's inability to achieve another pregnancy when the woman has already had one or more children.

According to Alexander (1982) and Crooks and Baur (1990), roughly 10 to 15 percent of couples wishing to have children are infertile. The figure increases to 25 percent if we include couples in which conception occurs but the woman is unable to carry the pregnancy to term, and couples unable to have any more children. According to Speroff et al. (1978) and Mosher (1988), some 40 percent of all infertility cases are attributable to physiological or other problems in the man, whereas 20 percent are due to factors present in both partners. Consequently, it appears that approximately two-thirds of infertility cases may be associated with male factors.

This document will provide an overview of the effects of licit and illicit drugs on the various physiological parameters related to infertility in couples. We will begin by discussing the abuse of illicit drugs that affect the central nervous system (CNS), such as morphine, cocaine, narcotics, and barbiturates. We shall then examine drugs that act on the autonomic nervous system (ANS): drugs for high blood pressure and medication prescribed for gastrointestinal illnesses. Next, we will briefly describe the effects of chemotherapy drugs and radiation on the reproductive system. Lastly, we will describe the effects of alcohol and of certain drugs in widespread use in our society: caffeine and nicotine (in the form of cigarettes).

Drugs

Drugs Affecting the Central Nervous System

The abuse of illicit drugs is so widespread today that it seems appropriate to call it a "social phenomenon." According to one sociodemographic study conducted in the United States, 22 percent of young adults aged 18 to 25 regularly smoke marijuana, 8 percent consume cocaine, 4 percent take various stimulants, and 1.6 percent take various hallucinogens. The percentages associated with other age groups are lower. In addition, 5 to 10 percent of American women of childbearing age use illicit drugs every day (Smith and Asch 1987).

The harmful effects of drug abuse on the functions of the male and female reproductive systems depend on a number of factors. First, the quantity and frequency of consumption as well as the degree of purity of the drugs are very important factors. Casual use causes much less fluctuation in sex hormone levels than daily use (see the list of sex hormones in the Appendix). The user's age and length of consumption are also important factors. Thus, frequent drug use during adolescence increases the risk of infertility significantly, whereas drug use during pregnancy increases the risk of spontaneous abortion. Lastly, the reproductive systems of people suffering from hypogonadism are more sensitive to the harmful effects of drugs (Smith and Asch 1987).

A number of classes of drugs may impair the normal functioning of the reproductive system. The major nerve tracts involved in the hypothalamic control of gonadotropins contain norepinephrine and dopamine neurotransmitters (Smith 1982; Smith and Asch 1987). Many pharmacological compounds may change the concentrations of these neurotransmitters by altering their synthesis, release, receptor activation, and reuptake by the presynaptic membrane. There are two groups of such drugs: the first, consisting of anaesthetics, analgesics, sedatives, and tranquillizers, inhibits CNS activity, while the second, consisting of anti-depressants, stimulants, and hallucinogens, stimulates it. Because of their action on the CNS, all these drugs can modify gonadotropin control exercised by the hypothalamic-pituitary axis. Consequently, changes in levels of the luteinizing (LH) and follicle-stimulating (FSH) hormones, and of prolactin (PRL), may be related to various abnormalities in the reproductive system.

Illicit Drugs

Marijuana

Marijuana is a CNS inhibitor composed of a number of psychoactive compounds, the main one of which is $\Delta 9$ -tetrahydrocannabinol (THC). This substance inhibits secretion of the pituitary hormones PRL, LH, and FSH, which in turn reduce sex hormone levels (Smith and Asch 1987).

Most of the research into the effects of marijuana and/or THC has been conducted on rhesus monkeys. According to Smith et al. (1979),

when administered in very high doses to female rhesus monkeys, THC reduces serum FSH and LH levels by 50 to 80 percent for approximately 24 hours. In light of these findings, a number of researchers then decided to examine the effects of marijuana consumption on the menstrual cycle of rhesus females. Using THC doses similar to those found in the blood of human marijuana consumers, Asch et al. (1981) discovered that THC impedes the normal menstrual cycle in rhesus females. If administered during the follicular phase, it inhibits ovulation. In addition, estrogen and progesterone remain at basal levels during the entire menstrual cycle, whereas they should fluctuate. The same authors (1979) administered identical doses of THC during the luteal phase and observed only*minor hormonal changes. However, in both experimental conditions (1979 and 1981), they observed a continuous disruption of ovulation, and of estrogen

It is also important to mention the relationship between continual intake of THC and the development of tolerance to the drug. In 1983, Smith et al. injected THC into female rhesus monkeys. Sex hormone levels became abnormal, and none of the females ovulated. After long-term administration of THC, a tolerance to the drug's inhibiting effects developed, and menstrual and hormonal cycles returned to normal.

and progesterone levels, which they say returned to normal only several

months after the THC was administered.

Similar results have been obtained in respect of young women who were regular marijuana users. According to Smith and Asch (1987), the luteal phases and menstrual cycles of these women were very short compared to those of women who had never smoked marijuana. In another study, a marked decline in LH levels was recorded during the luteal phase of young women who smoked marijuana every day (Mendelson et al. 1986). The same study also revealed the existence of an effective tolerance to the drug. Tolerance appeared in virtually the same way as observed in female rhesus monkeys. As a result, the authors observed that estrogen, progesterone, LH, and FSH levels returned to normal when the subjects developed a tolerance to THC.

Experiments conducted on male rhesus monkeys show that administration of THC over a long period or in high dosages results in a decline in serum testosterone levels, which lasts approximately 24 hours (Smith and Asch 1987). Furthermore, the rhesus males also developed a tolerance to THC. Contrary to the females, however, their sex hormone levels did not return to normal values (i.e., those recorded before the THC was administered). Among other things, testosterone levels remain relatively low once the tolerance phase begins (ibid.).

In men, the effects of marijuana on testosterone levels are difficult to assess. Some studies indicate that marijuana smoking over a long period results in a sharp decline in testosterone (Hembree 1988; Kolodny et al. 1974). According to Sobel et al. (1986), declines in serum testosterone levels occur in inverse proportion to the doses of marijuana inhaled, and the same is true of all incidences of sperm abnormalities. However, after

measuring serum testosterone levels before, during, and after chronic marijuana smoking, Mendelson et al. (1974) observed no significant fall in those levels. In an attempt to explain these contradictory findings, it should be pointed out that testosterone levels fluctuate considerably, even in men who do not smoke marijuana (Smith and Asch 1987). According to Hembree (1988), they may vary by 100 percent in a single day. Consequently, Hembree concludes that testosterone fluctuations associated with marijuana consumption probably have no significant effects on sperm

production.

Another aspect of the male reproductive system affected by drugs is spermatogenesis. Zimmerman et al. (1979) and Hembree (1988) have assessed the effects of THC and marijuana on spermatogenesis in rodents, while Dixit et al. (1977) conducted their research on dogs. All the research showed that administration of these drugs over long periods may cause a reduction in testicle size, degeneration in spermatogenesis, and morphologic abnormalities in spermatozoa. Hembree (1988) developed an animal model enabling him to distinguish between direct and indirect effects of inhaling marijuana. The findings from his experiments indicate that inhaling very large doses of the drug indirectly affects sperm production by suppressing sex hormone activity. Similar doses to those directly inhaled by humans produced a degeneration in the germinal epithelium, although this did not cause significant hormonal changes. Lastly, Hembree was unable to associate chronic exposure to marijuana with any significant decline in testosterone levels or gonadotropin production. Furthermore, although this last experimental condition caused reduced sperm production in rats, no decline in fertility was recorded. This was one of the rare experiments in which animals have inhaled marijuana. experiments, the drug is administered by intramuscular or intravenous injection. In such cases, it is risky to extrapolate the effects of the drug on animals to humans.

Hembree et al. (1976), Relman (1982), and Hembree (1988) have noted similar effects to those observed in animals in men who are regular marijuana users (200 mg of THC per day over a four-week period). They recorded cases of asthenospermia, morphologic abnormalities in spermatozoa, oligospermia, and reduced sperm production. Everything returned to normal three to four weeks after the experiment.

Although these findings are a rich source of information, they are difficult to interpret. Spermatogenesis requires approximately 76 days (Smith 1982; Smith and Asch 1987). Furthermore, marijuana is made up of a number of pharmacological compounds. Consequently, it is possible that one or even several of them act only on the first stages of sperm production and have no discernible effects for a number of weeks. The final stages of spermatogenesis are relatively well protected from external toxins by the blood-testicle barrier. It is thus very difficult to predict or even

evaluate the extent of testicular toxicity caused by certain drugs such as marijuana.

Despite all these studies, it appears impossible to state that marijuana or one of its components causes infertility in men or women. At the very most, this drug may delay conception. Whether its effects on sperm production are reversible is not known. According to Sobel et al. (1986), an interruption in marijuana consumption causes a rapid increase in testosterone levels. No comparable study has been conducted to assess the consequences of such an interruption on ovarian dysfunction in women. Furthermore, the diachronic studies that have focussed on this problem in men only were conducted over periods of time that were much too short. It is therefore difficult to assess the impact of interruptions in marijuana consumption on sperm production and, ultimately, on the fertility of the couple. Furthermore, the following two points should certainly not be forgotten in this regard: first, an average of four months of normal sperm production is required to achieve conception, and, second, during every normal menstrual cycle, there is only a 20 percent chance of conception in fertile couples (Hembree 1988).

Couples wishing to conceive should limit their marijuana consumption considerably, if not stop it altogether (Berkowitz 1986; Smith and Asch 1987). This advice seems all the more appropriate since THC can easily penetrate the placenta and reach the fetus if inhaled during pregnancy. To date, there is no research evidence indicating that THC or marijuana increases the incidence of spontaneous abortion, stillbirths, or genetic abnormalities (Julien 1981). However, no large-scale studies over long periods have been conducted.

Cocaine

Cocaine is a CNS stimulant acting mainly on the catecholamine transmitters (i.e., dopamine and norepinephrine). It acts as a local anaesthetic by inhibiting peripheral nerve conduction and preventing norepinephrine and dopamine reuptake by the presynaptic membrane. Increased concentrations of norepinephrine at the nerve endings cause vasoconstriction, increased blood pressure, and tachycardia (Smith and Asch 1987; Bracken et al. 1990).

According to Smith and Asch (1987), cocaine temporarily increases sexual excitement. Like a local anaesthetic, it can prolong erection and delay ejaculation if applied to the genitals of both the man and woman. Since cocaine suppresses all inhibitions, some claim it has aphrodisiac properties.

In the United States, 30 percent of men between the ages of 26 and 34 claim to have taken cocaine at least once in their life, whereas 5 percent consume it regularly every month (Smith and Asch 1987).

Experiments conducted on rats (Gordon et al. 1980) and on male rhesus monkeys (Scher et al. 1982, cited in Bracken et al. 1990) revealed that low doses of cocaine cause increased LH and testosterone levels in

subjects, while high doses inhibit the secretion of LH, thus considerably reducing testosterone levels. In similar experimental conditions, Steger et al. (1981) administered cocaine to female rats. They observed variations in LH levels comparable to those reported by Gordon et al. (1980). In addition, Steger et al. (1981) reported that, contrary to PRL, blood levels of which fell when cocaine was administered, FSH levels were not affected. According to Smith and Asch (1987), the increases in LH and reduction in PRL levels could be attributed to the large quantity of norepinephrine in the synaptic cleft and/or to the inhibiting action of dopamine on these hormones.

As noted above, testosterone is needed for normal spermatogenesis. Studies by Gordon et al. (1980) and Scher et al. (1982, cited in Bracken et al. 1990) showed that cocaine alters serum testosterone levels in animals. According to Sever and Hessol (1985), cocaine and its metabolites cause similar effects in humans, and they also directly affect the first stages of spermatogenesis. Phillips et al. (1985) suggest that vasoconstriction caused by cocaine may have harmful effects on testicle function.

One of the most recent studies evaluating the effects of cocaine on sperm characteristics was conducted by Michael Bracken and his associates in 1990. These authors interviewed 1 309 men concerning their use of licit and illicit drugs. They also gathered data on sperm concentrations, motility, and morphology as measured in the first sperm analysis. Other variables such as varicocele, cryptorchidia, and hernias were also included in a multiple regression analysis. The results of that analysis showed a strong association between cocaine consumption over a period of two years and both low sperm production and a higher incidence of infertility in men as compared to a population that had never used cocaine. Cocaine consumption over a minimum period of five years is linked to low sperm production and motility, greater morphologic abnormalities in spermatozoa, and a high infertility rate. The authors also obtained strong correlations between infertility and casual cocaine use over several years, and between infertility and frequent cocaine use over a limited period of time.

Few studies have assessed the effects of cocaine use during pregnancy, although Chasnoff et al. (1985) and Pond et al. (1985) recorded a spontaneous abortion rate of 38 percent in a group of cocaine addicts as compared to a near-zero rate in the control group.

Narcotics

Before describing the effects of narcotics on reproduction, some background information is necessary. First, the term "narcotics" is inappropriate, as "narcosis" means an induced state of unconsciousness, and all the substances called "narcotics" that are derived from opium produce a state of analgesia that is not accompanied by a loss of consciousness. This is why the term "narcotic analgesics" is used in most

pharmacology books. Narcotic analgesics are a group of compounds that, in addition to their effect in decreasing pain, have sedative, mood-elevating, and anxiety-reducing properties. They induce depressed breathing function and also result in tolerance and dependence. They also inhibit electrical activity in certain regions of the CNS, including the hypothalamus. This inhibition results in, among other things, lower production of dopamine and norepinephrine neurotransmitters. As we have already mentioned several times, the hypothalamus, dopamine, and norepinephrine play leading roles in the reproductive system.

Narcotic analgesics have their main effect through the hypothalamic-pituitary axis. As a result, changes in gonadal function are almost inevitable, and such changes are reportedly responsible for lower sex drive and sexual performance (Smith 1982; Smith and Asch 1987). According to Berkowitz (1986), many narcotics abusers suffer from erectile inhibition or frigidity. In addition, menstrual irregularities, and even infertility in men and women, are associated with excessive use of narcotic analgesics (Smith 1982; Smith and Asch 1987).

The two most frequently used narcotic analgesics are morphine and heroin. Male heroin addicts have atrophied accessory sex organs, and some are infertile or experience erectile inhibition (Sobel et al. 1986). Similar results have been observed in rats that had received a number of heroin injections. A decline in the weight of the prostate and seminal vesicles was observed in these animals (Smith and Asch 1987). These disturbances in the male reproductive system are associated with hormonal changes. However, the specific nature of those changes is not clearly established. Some researchers report increased serum LH and FSH levels in men who have consumed heroin (Kley et al. 1977), whereas others have observed significant declines in those hormones (Brambilla et al. 1979).

Heroin completely disrupts the estrous cycle in rats and the menstrual cycle in women. Consequently, ovulation becomes very unlikely (Gaulden et al. 1964; Stoffer 1968). According to Sobel et al. (1986), 85 percent of women who are dependent on anaesthetic analgesics experience major menstrual disorders, and 90 percent of them are infertile. Morphine use affects both female rats and women in the same way as heroin. Significant reductions in serum LH and FSH levels were recorded in both female rats and women addicted to heroin and morphine (Smith and Asch 1987). In 1983, Gilbeau et al. injected morphine in male rhesus monkeys. They then observed a significant decline in LH levels followed by an equally significant reduction in testosterone levels and asthenospermia. However, these authors did not directly assess the monkeys' fertility. According to Smith and Asch (1987), the fertility of most morphine addicts appears to be greatly reduced, if not non-existent.

Few studies have been conducted on the effects of consumption of narcotic analgesics during pregnancy. According to Julien (1981), however, the use of naloxone (an antagonist of narcotic analgesics) can lessen the depressed breathing observed in mothers who have taken the drugs during

pregnancy, and in their newborn babies. As morphine and heroin pass easily through the placenta, any breathing difficulty experienced by the mother may affect the normal development of the fetus.

Licit Drugs

Barbiturates

Barbiturates are sedative and hypnotic agents. They reduce neuron activity in a number of regions of the CNS. According to Smith and Asch (1987), this sedative property makes them very "popular" among young adults, who form the population most likely to abuse them.

Barbiturates such as phenobarbital have been used as anaesthetics in studies of animal reproduction for a number of years. These drugs inhibit LH and FSH secretion and subsequently cause a decline in sex hormone levels in female rats and hamsters (Everett and Sawyer 1950, cited in Smith and Asch 1987; Siegel et al. 1976). It is important to point out, however, that LH secretion in these animals depends on a light-dark cycle. Extended barbiturate-induced anaesthesia did not cause LH inhibition in female rhesus monkeys (Knobil 1974), although the authors reported lower rates of this hormone. Smith and Asch (1987) state that barbiturate injections produce similar effects in male and female animals. In women, barbiturate consumption is linked with menstrual abnormalities (Berkowitz 1986). To the best of our knowledge, no study has focussed on the effects of barbiturates on the male reproductive system.

Phencyclidine hydrochloride (PCP) was first used as an anaesthetic and tranquillizer for animals. PCP, or "angel dust," has been recognized as an illicit drug since 1978. PCP abuse appears to be widespread (Smith and Asch 1987). The drug has hallucinogenic effects, and it alters metabolism and the concentration of a number of neurotransmitters in various regions of the CNS, including the hypothalamus.

If administered in moderate doses over extended periods of time, PCP and ketamine (a PCP analogue) do not produce significant fluctuations in serum testosterone, LH, or PRL levels in male rhesus monkeys (Zaidi et al. 1982). However, when administered in doses similar to those used by humans, PCP significantly lowered serum LH and testosterone levels in rats treated over nine days (Harclerode et al. 1984). Immediately after treatment was discontinued, levels of these hormones reached significantly higher values than those of the rats in the control group. Serum LH and testosterone returned to normal levels only 60 days after treatment was discontinued in adult male rats and after 80 days in juvenile male rats. PCP therefore seems to have effects on sex hormones that extend well beyond the specific time of absorption.

How the use of "angel dust" affects human sex hormones is not yet known (Smith and Asch 1987), and even less is known about its effect on human fertility. According to Julien (1981), however, barbiturates and anaesthetics pass through the placenta very easily. For example, if barbiturates are injected into the mother intravenously during her

contractions, a significant quantity is also distributed to the fetus. Ten minutes after the injection, barbiturate blood levels are virtually identical in the mother and in the fetus. Children born to mothers who gave birth under general anaesthetic are often much less active than those of mothers who did not undergo such treatment.

Anti-Depressants and Neuroleptics

No systematic studies have been conducted on the secondary effects of anti-depressants or neuroleptics (anti-psychotics) on male or female fertility.

Sobel et al. (1986) very briefly mention that most anti-depressants (e.g., amitryptiline and imipramine, and diazepam, which is better known as Valium[®]) may cause ejaculatory and/or erection problems in men, and menstrual abnormalities in women (Berkowitz 1986).

As for neuroleptics (chlorpromazine and haloperidol), they reportedly cause a decline in sperm content and volume (Sobel et al. 1986). The side-effects of neuroleptics on the female reproductive system or on fertility are unknown, as they were not examined in any of the studies surveyed for this paper.

Licit Drugs Affecting the Autonomic Nervous System

The drugs most likely to affect sexual functions are those that affect the ANS (sympathetic and parasympathetic). In men, for example, erection and ejaculation depend on the control exercised by this system. The reflexes initiated by tactile stimulation in the genital area are transmitted via the internal pudendal nerve to the spinal cord. The efferent impulses transmitted by the parasympathetic fibres of the sacral region initiate the erection. Sperm emission is controlled by the parasympathetic fibres of the lumbar region. This response induces a contraction of the seminal vesicles and of the vas deferens and triggers contractions of the bulbospongiosus muscles, which causes ejaculation.

Sexual stimuli in women travel through the same nerve pathways as in men. The sensory nerve impulses travel to the lumbar and sacral regions of the spinal cord and from there to the brain. The motor impulses travel by the sympathetic and parasympathetic fibres of the ANS and cause the various physiological changes associated with sexual stimulation (e.g., vaginal lubrication results from increased mucus secretion by the glands located near the cervix).

Anti-Hypertensive Drugs

According to Sobel et al. (1986), side-effects of drugs designed to control high blood pressure include difficulty in achieving orgasm, loss of sexual desire, and difficulty in achieving or maintaining erection. According to Smith (1982), most anti-hypertensive agents may be associated with the development of erectile inhibition and ejaculatory incapacity. These medications may alter sexual functions by modifying

paragraphs.

autonomic transmission. However, it is difficult to evaluate the exact impact of their side-effects on the male and female reproductive systems because high blood pressure is frequently treated with "cocktails," or combinations of a number of anti-hypertensive drugs. In addition, studies designed to determine the effects of these drugs on the female reproductive system are virtually non-existent. We will be describing the secondary effects of the ingestion of certain anti-hypertensive drugs over the next few

Methyldopa and clonidine cause changes in norepinephrine levels in the ANS. They reduce blood pressure and electric transmission in the vasopressure centres of the brain stem. They also act peripherally. Thus, methyldopa may also induce sedation and reduce sex drive. The rate of erectile inhibition associated with methyldopa is about 30 percent, whereas it is only 4 percent in a control group (Smith 1982). According to Smith, the lower percentages reported in certain studies are an indication of less frequent sexual relations. In addition, increases in serum PRL caused by methyldopa can directly disrupt testicle function. As for clonidine, in addition to causing peripheral blood vessel dilation, it causes an increase in the incidence of men suffering from erectile inhibition (which ranges from 10 to 20 percent depending on the dose administered [Smith 1982; Smith and Asch 1987]).

Lastly, reserpine is a sympatholytic anti-hypertensive agent, which blocks dopamine receptors. Consequently, if prescribed in excessive doses, it can bring on symptoms of parkinsonian syndrome. According to Smith (1982), the side-effects of reserpine on sexual functions are similar to those of methyldopa. A decline in sex drive, increased erectile inhibition rates, and poor testicle function (due in part to reduced PRL levels) may affect men who take this medication.

Spironolactone is the only anti-hypertensive drug in respect of which side-effects on female sexual functions have been studied. The drug is an anti-aldosterone diuretic. As a result of its antagonistic action to aldosterone, it may cause reduced sex drive, erectile inhibition, gynaecomastia, and inhibited testosterone production in men. In women, high endogenous estrogen levels explain why spironolactone becomes an estrogen antagonist and causes menstrual problems. Consequently, according to Sobel et al. (1986), the differences in endogenous estrogen and testosterone levels and in the mammary or testicular receptor systems determine the final effect of spironolactone.

These few anti-hypertensive drugs represent only a portion of those prescribed by physicians. According to Smith (1982), it is difficult to say with any certainty that the greater incidence of erectile inhibition and menstrual disorders associated with the use of these drugs constitutes major side-effects. In fact, cardiovascular complications due to changes in blood pressure can have similar effects. Consequently, further study on the matter is required.

Drugs Prescribed for Gastrointestinal Illnesses

Androgenous hormones (testosterone, estrogen, and progesterone) are catabolized in the liver and eliminated in urine. Every gastrointestinal illness therefore has the potential to alter concentrations of these hormones and affect the reproductive system.

Cimetidine is a histamine antagonist. It slows blood flow to the liver and inhibits the oxidative metabolism of a number of other drugs, such as propanolol and diazepam (Valium®). It is often prescribed for long-term liver diseases. Cimetidine reduces the secretion of basal gastric acid, and gastric acid secretion stimulated by food, by approximately 90 percent. It also cures gastric and duodenal ulcers. Although it is highly effective, cimetidine nevertheless has harmful anti-androgenic side-effects on the reproductive system, including sexual dysfunction and limited sperm production (Sobel et al. 1986). Sobel et al. also report that, in a group of fertile males suffering from liver disorders who were treated with cimetidine over nine weeks, sperm production decreased significantly. The gonadalpituitary axis in men and women treated with cimetidine has not yet been systematically evaluated. It must be noted that studies concerning the potential effects of medication prescribed for gastrointestinal illnesses on reproductive function are also lacking. Furthermore, the few studies conducted so far have concerned cimetidine, but it is not the only medication prescribed for such illnesses. In addition, research assessing the effects of these drugs on the female reproductive system and the fetus during pregnancy is virtually non-existent.

Chemotherapy: Drugs and Radiation

Today, advances in a number of scientific fields enable many persons suffering from malignant diseases to survive. But what happens to the fertility of these patients?

Cancerous cells generally divide very quickly. They are the targets of anti-cancer drugs, which inhibit their division and suppress various stages of protein synthesis (Smith 1982). However, the toxic effects of these drugs also affect other cells, including the cells of the germinal epithelium and glandular cells in the accessory sexual organs, which divide quickly.

There are a number of reasons why a discussion of sexual dysfunction associated with cancer therapies is delicate. First, there are many types of malignant diseases requiring a variety of treatments. Second, the duration of those treatments varies with the stage of the disease. Lastly, people of all ages can have cancer, which means that the various therapies will affect their reproductive systems differently. Despite all these reservations, it is nevertheless possible to draw several conclusions as to the side-effects of chemotherapy and radiation treatments.

According to Schilsky et al. (1980), radiation and chemotherapy cause amenorrhoea over long periods of time. These therapies are also associated with increased gonadotropin levels, and even with menopause symptoms. However, they do not cause permanent infertility. Discontinuation of these

treatments may result in the restoration of a relatively normal menstrual cycle, and may even permit gestation (Horning et al. 1981; Baker et al. 1972). However, the woman's age at the time of chemotherapy or radiation treatment is an important factor (Horning et al. 1981). The return of regular menstruation and the probability of pregnancy are inversely related to the patient's age. In other words, the younger a woman is, the more likely she is to return to a normal menstrual cycle. After 30 years of age, this probability decreases quickly. According to Baker et al. (1972), chemotherapy or radiation treatment may even cause permanent infertility in women over 40. According to Horning et al. (1981), the doses used in chemotherapy do not appear to be related to infertility, although Morgenfeld et al. (1972) say the contrary. Lastly, a woman undergoing combined chemotherapy and radiation treatment will experience major hormonal imbalances. Only 20 percent of women undergoing such treatment return to regular menstrual cycles (Horning et al. 1981).

The impact of radiation and chemotherapy during pregnancy varies depending on dose. Effects may include pregnancy loss or teratogenic

effects on the fetus, such as microcephaly.

In men, chemotherapy may damage the germinal epithelium of the testicles and may cause azoospermia. According to Sherins and DeVita (1973), chemotherapy administered over four months invariably causes azoospermia problems and limits sperm production. Spermatogenesis is thus considerably reduced and returns to normal values only several years after treatment is discontinued. According to Kirkland et al. (1976), pubescent male gonads are affected the most by chemotherapy. In short, infertility caused by various chemotherapy agents is very common. It generally lasts five years after chemotherapy is completed, but is not permanent (Smith 1982). Sex drive, secondary sexual characteristics, and testosterone levels are often altered less than fertility, since the gonadotropins appear to be more resistant than the germinal epithelium to the effects of the various drugs.

As far as we know, no studies have been conducted on the effects of radiation on the male reproductive system.

Alcohol

According to two studies conducted by researchers at the National Institute of Mental Health in the United States, alcohol abuse and dependency are the two most common psychiatric disorders (Myers et al. 1984; Robins et al. 1984), even more common than phobias, depressions, and various forms of substance addiction. They are the leading psychiatric disorders among men aged 18 to 64. Alcohol abuse and dependency are less acute problems among women. They are the fourth most frequently diagnosed psychiatric disorder among women aged 18 to 24.

In addition to its numerous physical, psychological, social, and economic consequences, alcohol abuse causes major disorders in the reproductive system that can cause infertility in both men and women. A number of researchers have confirmed the existence of a significant relationship between chronic alcohol abuse and its harmful effects on the male reproductive function (Anderson et al. 1983; Cicero 1982; Sobel et al. 1986; Smith 1982; Smith and Asch 1987). According to Cicero (1982) and Farkas and Rosen (1976), excessive alcohol consumption can be likened to "chemical castration" and is one of the most common causes of erectile inhibition. This condition may become permanent, even in former alcoholics who have been dry for several years (Lemere and Smith 1973). In addition, roughly 80 percent of alcoholic men are diagnosed as infertile and suffer from atrophied seminiferous tubules, sperm abnormalities, and lower sperm production (Sobel et al. 1986). According to Mendelson et al. (1977), Cicero (1982), Sobel et al. (1986), and Smith (1982), alcohol first affects testosterone synthesis and secretion in the testicles. Incidentally, alcohol and its principal metabolite, acetaldehyde, inhibit enzymes involved in testosterone synthesis. As we noted in the section on gastrointestinal illnesses, testosterone is metabolized in the liver. Alcohol increases liver metabolism of this hormone (Gordon et al. 1976; Smith 1982). It should be pointed out, however, that this reduction in testosterone does not come only after years of cirrhosis or alcoholism, as alcohol may considerably reduce testosterone levels even in men who suffer from no form of liver disease (Sobel et al. 1986). Gordon et al. (1976) reported significant reductions in testosterone in normal men after only a few months of daily alcohol consumption. In addition to altering testosterone synthesis and secretion, alcohol reduces testicle weight (Klassen and Persaud 1978) and serum LH levels (Cicero and Badger 1977). It may also result in increased PRL levels and gynaecomastia. Researchers generally agree that the testicular atrophy and demasculinization observed in chronic alcoholics are mainly due to the direct toxic effects of alcohol rather than to disorders in estrogen metabolism resulting from liver disease. Reduced testosterone levels are accompanied by increased activity in the liver's estrogen receptors (Lester et al. 1979).

Researchers do not know the critical quantity or duration of alcohol consumption that may cause infertility. In 1983, Anderson et al. developed an animal model designed to answer this question. They injected two different concentrations of ethyl alcohol into male mice. To evaluate the mice's fertility, they analyzed the quantity and quality of the spermatozoa that entered the female's reproductive canal. Depending on the concentration and duration of administration of ethyl alcohol, Anderson et al. (1983) observed a gradual drop in the speed of the spermatozoa, although the percentage of mobile spermatozoa remained unchanged. According to the authors, these findings indicate that sperm mobility in itself is not an accurate indicator of fertility. They also observed that injections of 5 percent ethyl alcohol solution over 5 to 10 weeks produced

a significant increase in sperm content, whereas the same concentration administered over 20 weeks induced a significant decline. According to Prins and Zaneveld (1979) and Anderson et al. (1983), this biphase effect reflects the redistribution of spermatozoa already present in the vas deferens and depends on its contraction, which is controlled by norepinephrine. Degani et al. (1979) observed that ethyl alcohol induces increased spontaneous release of norepinephrine in the vas deferens in rabbits.

Anderson et al. (1983) also reported a drop in sperm content in the epididymis and attributed it to a reduction in spermatogenesis. According to the authors, testicular atrophy and low-quality spermatogenesis in the seminiferous tubules in mice receiving injections of a 5 percent ethyl alcohol solution over 20 weeks or a 6 percent solution over five weeks

clearly attest to this.

In these last two experiments, a high percentage of spermatozoa with morphologic abnormalities was observed. According to Sherins et al. (1977), there is a negative correlation between the frequency of spermatozoa with abnormal heads and the probability that the ovum will be fertilized. Anderson et al. (1983) also reported a higher than normal number of spermatids in the seminiferous tubules. These immature cells are incapable of fertilizing eggs. The authors also noted similar immaturity in spermatozoa in the epididymis. According to Mann and Lutwak-Mann (1981) and King and Fabro (1983), the maturity of spermatozoa in the epididymis is an essential criterion of fertility.

All these results strongly suggest that chronic ethyl alcohol administration in male animals and excessive alcohol consumption by men are

significantly related to infertility.

Compared to the number of studies on the effects of alcohol on the male reproductive system, relatively little research has focussed on its effects on women. As Belfer et al. mentioned in 1971, the neuro-psychophysiological characteristics of women who consume excessive amounts of alcohol remain relatively unknown. Twenty years later, we could say the same thing. Other studies have of course been conducted since that time, but there are still a number of questions to be answered.

Most of the research indicates that alcohol intoxication causes irregularities in the menstrual cycle, dysmenorrhoea (Wilsnack et al. 1984), and even amenorrhoea and anovulation (Hugues et al. 1980). In addition, according to Wilsnack et al. (1984), women who drink more than six glasses of alcoholic beverages over a maximum period of five days are more likely to experience obstetrical disorders and to have to undergo gynaecological surgery other than hysterectomies. Lastly, according to Wilsnack (1973), chronic alcohol consumption and alcoholism may cause infertility in women. However, according to Olsen et al. (1983), moderate alcohol consumption does not appear to be related to female infertility.

Wilsnack et al. (1984) observed that it is particularly difficult to dissociate the effects of malnutrition and alcohol-related liver disease from the direct toxic effects of alcohol in women. Malnutrition accompanied by

considerable weight loss or liver dysfunction also cause menstrual irregularities, even in women who do not consume alcohol. To control these variables, Mello et al. (1983) developed an animal model using female macaque monkeys. They observed that monkeys self-administering large doses of alcohol over periods ranging between three and six months experienced problems of amenorrhoea, uterine atrophy, reduced ovarian mass, and slightly lower LH levels. According to the authors, these symptoms correspond to those of alcoholic women. Consequently, it appears that alcohol toxicity is responsible for irregularities in the menstrual cycle, as the researchers were able to control the other nutritional variables that could contaminate the results of the experiment. Other studies have failed to confirm the findings of Mello et al. (1983) as regards the drop in LH levels. Mendelson et al. (1981), McNamee et al. (1979), and Mello et al. (1984) found that chronic alcohol ingestion does not suppress pituitary gonadotropins either in female rhesus monkeys or in women. Whatever the case may be, this discrepancy in results is not a critical factor, as Mello et al. (1983) observed only a slight reduction in LH levels. What seems more surprising, however, is the absence or virtual absence of hormonal changes in women who drink large quantities of alcohol, whereas, as we mentioned above, chronic alcohol ingestion significantly reduces testosterone levels. In light of these findings, Mello (1987) emphasized the need to develop more sophisticated tests to evaluate the toxic effects of alcohol on female fertility more accurately.

Alcohol consumption during pregnancy represents a major risk. Women who consume more than three ounces of alcohol per day experience twice as many spontaneous abortions as women who consume none (King and Fabro 1983; Harlap and Shiono 1980; Sokol 1980). In addition, alcohol has teratogenic effects. Children born of mothers who had high blood alcohol levels during the critical stages of fetal development may be afflicted with fetal alcohol syndrome (King and Fabro 1983). These children suffer from mental retardation, slow physical growth, and congenital deformities. According to Julien (1981), fetal alcohol syndrome is the third most frequently observed cause of congenital deformities and mental retardation in newborns, behind trisomy 21 and spina bifida.

Caffeine

Caffeine is the most frequently used licit drug in the world. It is also a methylxanthine often prescribed to treat asthma and other pulmonary disorders. Caffeine particularly affects the CNS, causing slight cortical arousal characterized by increased alertness and deferral of fatigue (Boushey and Holtzman 1987).

Contrary to popular belief, caffeine is not found solely in coffee. Tea, cocoa, and colas also contain caffeine (Gilbert et al. 1976). High caffeine

consumption may disturb sleep and cause cardiac arrhythmia, particularly in the elderly. There even exists a caffeine rejection syndrome, which is characterized by lethargy, irritability, and headaches. This syndrome may appear after ingestion of the equivalent of six cups of coffee (Hollister 1987).

Caffeine circulates rapidly through all tissues of the human body. The same phenomenon is observed in animals. As there appears to be no physiological barrier to its movement, caffeine can be detected in the brain. testicles, uterine secretions, blastocytes, fetal tissue, amniotic fluid, and even mother's milk (Wilcox et al. 1988; Bonati et al. 1984-85; Sieber and Fabro 1971; Goldstein and Warren 1962). According to Wilcox et al. (1988), caffeine disrupts the reproductive capacities of most animals, although it is risky to extrapolate this observation to humans since caffeine metabolism varies considerably from species to species. For example, the main caffeine metabolite in human beings and rabbits is paraxanthine, which is found in very large quantities in the blood of both species. Theophylline is the major caffeine metabolite found in the macaque monkey, while theobromine is found in large quantities in the blood of mice (Bonati et al. 1984-85). Furthermore, according to the same authors, rabbits, mice, and rats metabolize caffeine two to three times more quickly than human beings. Given the findings of this study, we will not here present the studies conducted on animals.

In 1988, Wilcox and colleagues interviewed 104 women concerning their caffeine consumption. Ninety-seven percent of them had drunk caffeinated beverages during the period when they had tried to conceive. During subsequent menstrual cycles, those who had consumed large quantities of caffeine (group 1) were less likely to become pregnant than those who had ingested very small quantities of the drug (group 2). The risk of infertility (i.e., the inability to conceive during a period of roughly 12 months) was five times greater in the first group. According to the authors, infertility rates depend on the doses of caffeine ingested. In summary, Wilcox et al. (1988) demonstrated that the women in their study who drank more than two cups of ground coffee per day (or the equivalent) were half as likely to become pregnant as those who consumed smaller amounts.

Cramer (1990) notes that the side-effects on human fertility of tannic acid, which is found in coffee, tea, cocoa, and red wine, have never been studied. According to McKee (1889), the college of druids in the twelfth century considered this acid to be a potential factor in infertility. Tannic acid is therefore a substance to which greater attention will have to be paid in future research.

In our survey of the literature, we were unable to find papers on the effects of caffeine on male and female sex hormones. According to Marshburn et al. (1989), caffeine consumption is associated with higher sperm counts, and moderate consumption of caffeine increases sperm motility. These two factors would therefore tend to increase, rather than decrease, male fertility.

The influence of caffeine on fetal development is of great interest, as it is one of the drugs ingested most frequently by pregnant women. Caffeine has mutagenic and teratogenic properties in animals. It also increases the circulation of catecholamines and can as a result cause constricted blood vessels in the uterus and placenta.

Furuhashi et al. (1985) monitored more than 9 900 pregnant women for more than 24 weeks of gestation. They found the risk of spontaneous abortion to be high among women who drink more than five cups of coffee per day. Women in this group often experience contractions early in their pregnancy, and their fetuses are small relative to gestation age. Among women who consume very large quantities of coffee (i.e., more than five cups per day), the authors observed high rates of spontaneous abortion, chromosomal abnormalities, and multiple congenital abnormalities in the fetus. The results of a study conducted by Linn et al. (1982) contradicted those of Furuhashi et al. (1985), as they noted that caffeine consumption during pregnancy has a minimal effect on the fetus. It is important to point out, however, that, contrary to Furuhashi et al. (1985), Linn et al. (1982) used a logistical regression in analyzing their findings and attempted to control the following variables: cigarette smoking, demographic characteristics, and the medical history of the women interviewed. We find it interesting that, before submitting their findings to the regression analysis, the researchers indicated that the women who drank more than four cups of coffee a day experienced shorter gestation and delivered underweight children. These results are comparable to what was reported by Furuhashi et al. (1985). As regression analysis makes it possible to sort out the harmful effects of various factors on pregnancy, it should be used more often. Given the relatively limited number of studies in the area, several authors advise pregnant women and those wishing to become pregnant to limit their caffeine consumption (Julien 1981; Gilbert et al. 1976; Furuhashi et al. 1985).

Tobacco

Despite all the anti-tobacco campaigns in recent years, the percentage of men and young women who smoke remains relatively high in both the United States and Canada. A census conducted by the U.S. Department of Health and Human Services (1984) revealed that roughly 30 percent of women and 36 percent of men smoke. Cigarette smoke contains several toxins, including nicotine and carbon monoxide, as well as recognized carcinogenic and mutagenic substances such as radioactive polonium, benzopyrene, dimethylbenzanthracene, dimethylnitrosamine, naphthalene, and methylnaphthalene (Stedman 1968). Direct and indirect inhalation of cigarette smoke occurs through pulmonary vasculation and blood circulation throughout the body (Stillman et al. 1986) and may cause lung

cancer, cardiac complications, and emphysema. Smoking women over 35 years of age who use oral contraceptives are more prone to arteriosclerotic and cardiovascular diseases than non-smokers (Wentz 1986).

Given the large number of harmful effects of cigarette smoking, it would have been surprising if it did not also affect the reproductive system. Research conducted on male rats and mice has shown that nicotine, cigarette smoke, and polycyclical aromatic hydrocarbons produce testicular atrophy, block spermatogenesis, and alter sperm morphology (Viczian 1968; Wyrobek and Bruce 1975). Studies on female rats and mice suggest that nicotine and cigarette smoke alter the mobility of the reproductive canal and may in this way prevent embryo implantation; high infertility rates were recorded among these females (Essenberg et al. 1951; Thienes 1960, all cited in Mattison 1982).

The studies on the effects of cigarette smoking on men have produced contradictory findings. Some researchers state that cigarette smoke significantly reduces sperm density, volume, and motility and causes a significant increase in rates of abnormal sperm morphology (e.g., Marshburn et al. 1989; Stillman et al. 1986; Shaarawy and Mahmoud 1982), while others believe that it produces no significant changes in those physiological parameters (e.g., Close et al. 1990; Oldereid et al. 1989; Hoidas et al. 1985; Dikshit et al. 1987; Rodriguez-Rigau et al. 1982).

It is difficult to explain these contradictions. It is possible that the use of different sperm analysis techniques led to different conclusions (e.g., use of an electronic or optic microscope; little control over certain variables; insufficiently complex statistical analyses). With regard to this last element, Marshburn et al. (1989) emphasize the extreme importance of using a multifactorial analytical method. Using such a method, they were able to determine that simultaneous coffee and cigarette consumption causes a significant reduction in sperm motility and an equally significant increase in dead spermatozoa rates. These results therefore lead them to believe that cigarette smoke and coffee together represent a major risk of disrupting male fertility.

Few researchers have focussed on the endocrine profiles of smokers. Shaarawy and Mahmoud (1982) recorded significantly high FSH levels in smokers, while testosterone levels fell significantly and LH levels did not change at all. According to the authors, these findings indicate that the Leydig's cells synthesize less testosterone, which may result in low spermatogenesis. This hypothesis seems all the more likely since spermatogenesis may be directly affected by nicotine or catecholamines released in the body when a man smokes. Klevene and Balossi (1986) report that increased PRL levels are associated with cigarette smoke inhalation and with lower fertility in men. According to Sueldo et al. (1985), excessive PRL levels in the seminiferous tubules appear to inhibit the functional capacities of spermatozoa.

To sum up, it is difficult to draw conclusions from all this research. However, the often contradictory nature of the findings should encourage

men wishing to become fathers to exercise caution and limit their tobacco consumption.

In women, all the studies conclude that cigarette smoking disrupts the reproductive system enormously. According to Mattison (1982), the inhalation of cigarette smoke inhibits LH and PRL secretion and reduces secretions of growth hormone, vasopressin, and oxytocin. Mattison (1982) and Stillman et al. (1986) report that smoke inhalation causes increased menstrual abnormalities and may even bring on premature menopause. According to Mattison (1982), women who smoke experience premature menopause. Ex-smokers are likely to reach menopause at an age comparable to that of women who smoke fewer than 10 cigarettes a day. Consequently, stopping smoking does not appear to cancel the effects of tobacco on ovarian functions completely.

Smoking also increases genital secretion of the protein alpha 1-antitrypsin. Low levels of this protein enhance fertility by facilitating sperm migration or penetration. Consequently, excessive levels of alpha 1-antitrypsin significantly reduce female fertility. According to Ashley (1987), however, this effect appears to be reversible: in most cases, levels of this protein return to normal in women who stop smoking.

As for the effects of tobacco consumption on pregnancy, they are many in number: in addition to delaying conception (Baird and Wilcox 1985), tobacco consumption increases the risks of spontaneous abortion, perinatal death, and sudden infant death syndrome (Julien 1981; Stillman et al. 1986; Kline et al. 1983; Sandahl 1989). According to these authors, women over 30 years of age who smoke are at greater risk of aborting a trisomic child. King and Fabro (1983) and Stillman et al. (1986) add that women who smoke are more likely to deliver prematurely and to have underweight babies. In addition, according to Weinberg et al. (1989), women whose mothers smoked during pregnancy are substantially less fertile than those whose mothers did not.

Lastly, numerous studies associate tobacco consumption with female infertility rates greater than those recorded among non-smoking women (Ashley 1987; Howe et al. 1985; Olsen et al. 1983; Baird and Wilcox 1985; Phipps et al. 1987; Weinberg et al. 1989). According to Phipps et al. (1987), cigarette smoking is related to cervical and tubal infertility.

In conclusion, women wishing to have children should definitely refrain from smoking. Women who smoke during pregnancy should remember that their children then become passive smokers, since the components of cigarette smoke easily pass through the placenta (Julien 1981).

Conclusion

Most of the studies surveyed herein indicate that licit and illicit drugs can affect the physiological parameters linked to male and female fertility to varying degrees. However, none of them clearly demonstrates that any one of these drugs causes infertility. Consequently, considerable care should be taken in interpreting research into the effects of these drugs on fertility.

There are weaknesses or constraints, often inherent in the nature of experiments, in many of these studies. In many instances, however, it would be relatively easy to remedy the anaemic research effort in several fields of human reproduction research. While men and women are responsible for the infertility of couples in the same proportions (40 percent), there is a dearth of information concerning the consequences of various drugs on female fertility.

Furthermore, most findings of research conducted on the human population are based on epidemiological or retrospective studies, case histories, and interviews. This type of research has significant limitations. In such studies, researchers assume that the answers given by their subjects correspond to reality. Even if it is in their best interest, subjects may well choose not to disclose certain information or may simply forget to indicate major lifestyle characteristics (e.g., malnutrition, multiple drug use, fragile physical health). These variables may distort the results of physiological examinations (e.g., the post-coital test and hysterosalpingography) and lead to erroneous conclusions concerning the effects of certain drugs on the reproductive system. Consequently, the interviews and questionnaires to which subjects are submitted should possess adequate psychometric properties. This is not always the case, however. For example, Wilcox et al. (1988) themselves state that the validity and reliability of the questionnaire they used in their survey on caffeine consumption by women left something to be desired and that, consequently, the results they report must be interpreted with great care. Unfortunately, this is not an isolated example.

Infertility research is also limited by ethical considerations. It is often impossible to test the effects of drug abuse on the human population by applying a very rigid experimental method involving a control group (i.e., a group of subjects who do not receive the drug) and an experimental group (i.e., a group of subjects to whom a drug is administered). Research is therefore limited in many cases to correlational and descriptive studies of endocrine and physiological abnormalities, such as the characteristics of sperm and cervical mucus. Furthermore, some drugs, such as marijuana and tobacco, are composed of a number of toxic substances. It is therefore extremely difficult to identify the endocrinal-physiological effects on fertility of each such substance.

At the same time, it is impossible to overemphasize the need for experimental methods that lend themselves to multifactorial analysis.

Human beings do not live in antiseptic laboratories. Attempts must therefore be made to assess the impact of multiple variables that cannot be submitted to very strict experimental control. Furthermore, the majority of people dependent on licit and illicit drugs do not limit their consumption to only one of those drugs. For example, smokers are more likely to consume alcohol than non-smokers (Marshburn et al. 1989). Multiple drug use may have harmful effects that a simplistic statistical analysis cannot reveal.

Another weakness is the virtual non-existence of follow-up studies on the reversible effects of drugs on the male and female reproductive systems. Those that have been conducted focussed on a relatively short period of time. According to Smith (1982), because of the length of spermatogenesis and the many factors determining the characteristics of ejaculated sperm, follow-up studies should extend over some 6 to 12 months.

Research conducted on animals may make up for many of the weaknesses and constraints inherent in studies on the human population. Thus, it is possible to control certain variables (lifestyle, physical health, environment) and to apply a more rigorous experimental method (e.g., the use of control and experimental groups) to an animal population. According to Bonati et al. (1984-85) and Smith and Asch (1987), the best animal model for evaluating the effects of drug abuse on reproductive functions appears to be the monkey. Even if the metabolites of the various drugs are different in monkeys and in human beings, their pharmacokinetics is similar. Since human beings metabolize drugs much more slowly than some animals, such as rodents, it is risky to extrapolate conclusions from research conducted on rodents to human beings. Furthermore, according to Anderson et al. (1983), in vitro fertilization is the best way to assess the ability of spermatozoa to fertilize ova. Some drugs, such as alcohol, may alter sexual behaviour in the male, making it difficult to analyze male fertility adequately if the drug reduces sexual activity.

The first researchers to conduct laboratory experiments used much higher doses of drugs on animals than those used on humans, and these massive doses of drugs had devastating effects on reproductive systems (Smith and Asch 1987). Recent developments in biotechnology have made it possible to measure blood concentrations of drugs more effectively and to use doses that reflect human consumption models more accurately. The more we learn about the complex gonadal-hypothalamic-pituitary functions, the easier it will be to analyze the mechanisms triggered in those functions by drug use and abuse.

Scientific progress has also made it possible to achieve more accurate results in post-coital tests and to prescribe much more effective treatments. For many years, it was believed that the absence or virtual absence of mobile sperm in the vagina or cervical mucus was a criterion of male infertility (Smith 1982). Today, we know that there are two factors explaining the absence of mobile sperm: abnormal sperm production and abnormal vaginal or cervical secretions, which include low vaginal or cervical mucus production and the presence of sperm antibodies.

According to Smith, once secretion abnormalities have been corrected, the post-coital test becomes an extremely powerful tool because it makes it possible to determine sperm abnormalities very accurately.

Lastly, couples wishing to have children should limit their consumption of licit and illicit drugs, and even refrain from using them completely. The potentially harmful effects of drug use and abuse on fertility and on the fetus are numerous and argue in favour of prudence and moderation.

Appendix

The principal male sex hormones are testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). The gonadotropins LH and FSH are necessary for normal spermatogenesis and testosterone secretion. FSH stimulates spermatogenesis, LH testosterone secretion. Since testosterone is necessary for sperm production, LH may also be considered an important element in the process. FSH and LH production by the pituitary gland is stimulated by a releasing hormone produced by the hypothalamus. The testosterone produced by the testes prevents the release of LH through negative retroaction, but has little effect on FSH release.

The ovaries produce the female sex hormones, progesterone and the estrogens. The regulation of ovarian function involves the action of the gonadotropin-releasing hormones from the hypothalamus and the FSH and LH produced by the pituitary gland. The female sex hormones influence the secretion of releasing hormones, which in turn stimulate the secretion of FSH and LH.

Glossary

Abortion, **spontaneous**: Naturally occurring abortion, not caused by any local or general procedure; result of a pathology.

Amenorrhoea: Abnormal absence of menstruation.

Anaesthetics, local: Group of compounds that, when applied in appropriate concentrations to nerve tissue, block neuron conduction in a reversible manner.

Androgens: Generic term for a number of steroid hormones, mainly male.

Androgens: Generic term for a number of steroid hormones, mainly male. Androgens are synthesized and secreted mainly by the testes, but also by the adrenal cortex and the ovaries (in very small quantities). The principal testicular androgens are testosterone (the most active male hormone) and androsterone. They are metabolized in the liver and eliminated in the urine.

Antagonist: Antagonist drugs neutralize or counteract the effects of neurotransmitters on the postsynaptic cell.

Asthenospermia: Decline in sperm motility and duration of motility (less than 40 percent of mobile forms immediately or two hours after emission).

Autonomic nervous system (ANS): The set of nervous structures that control vegetative life (organ function and harmonization of the various organ functions), including the superior centres (located in the central nervous system) and the effector pathways (sympathetic and parasympathetic peripheral nervous system).

Axis, hypothalamic-pituitary: Anatomic-physiological concept based on the neuro-hormonal relations between the hypothalamus and the pituitary gland. The concept includes the notions of releasing hormones, inhibiting hormones, and neurocrinia.

Azoospermia: Absence of spermatozoa in the semen.

Blastocyte: An embryonic cell that has not yet become differentiated.

Brain stem: Region of the brain formed by the spinal bulb, the pons, and the cerebral peduncle, located in the posterior cranial fossa, in front of the cerebellum and the fourth ventricle.

Catabolism: Any destructive metabolic process by which organisms convert substances into excreted compounds.

Cells, germinal: Cells capable of dividing and differentiating; original cells in gametes that, in certain organisms, including vertebrates, separate early within the embryo.

Cells, Leydig's: Interstitial cells constituting the endocrine tissue of the testis; produce androgens, chiefly testosterone.

Central nervous system (CNS): Mass of nervous tissue composed of grey and white matter forming the brain and spinal cord, excluding the sensory, motor, and sympathetic and parasympathetic nerves that form the peripheral nervous system. **Cervicitis:** Infectious inflammation of the cervix.

Cervix: The front portion of the collum, or neck of the uterus leading to the vagina; contains numerous glands that produce vaginal mucus.

Chemotherapy: Generic term designating the treatment of disease by chemical agents. The term is used more particularly in reference to certain treatments for cancer and infection.

Cryptorchidism: A developmental defect characterized by failure of the testes to descend into the scrotum. In the case of bilateral cryptorchidism, the testes produce no sperm and the man is sterile. This form of sterility occurs because spermatogenesis cannot take place at the body's internal temperature. The scrotum allows the testicles to remain at a temperature lower than that of the body. The location of the testicles outside the abdominal-pelvic cavity thus appears necessary to the normal development of spermatozoa.

Dependence: Generic term covering the notions of physical dependence, psychological dependence, and substance dependence.

- 1. Physical dependence: new state of equilibrium that the addict appears to have found by means of drugs, but this equilibrium remains precarious, and the more spectacular manifestations occurring when the addict breaks this dependence are the symptoms of withdrawal.
- 2. Psychological dependence: constant desire to use a drug, to the point where the subject's behaviour is conditioned by that drug; psychological dependence appears to be independent of factors that characterize physical dependence.

3. Substance dependence: the sum of all physical and psychological phenomena that make certain drugs, after varying lengths of use, essential to a person's physiological equilibrium.

Diaphragm: Local contraceptive consisting of an intrauterine device.

Dysmenorrhoea: Painful menstruation.

Embryogenesis: The development of a new individual by means of sexual reproduction, that is, from a fertilized ovum; the process of embryo formation.

Endometriosis: A condition in which tissue more or less perfectly resembling the uterine mucous membrane (the endometrium) and containing typical endometrial granular and stromal elements occurs in various locations in the pelvic cavity.

Endorphins: Any of three neuropeptides present in the various structures of the central nervous system. They possess properties similar to those of substances that have the same action as morphine. All have potent analgesic activity.

Epididymis: The elongated cordlike structure along the posterior border of the testis, whose elongated coil duct provides for storage, transit, and maturation of spermatozoa.

Epithelium: The non-vascularized covering of internal and external surfaces of the body, including the lining of vessels and other small cavities.

Estrogens: Group of hormonal steroids. In women, natural estrogens are elaborated in the ovarian follicles and in the placenta during pregnancy; in men, in the testes.

Gamete: Generic term for any reproductive cell, male (spermatozoon) or female (ovum) before fertilization. Synonym: sex cell.

Gametogenesis: The development of the male and female cells, or gametes.

Gland, Bartholin's: One of the two small bodies on either side of the vaginal orifice, homologues of the bulbourethral glands in the male.

Gonad: A gamete-producing gland; an ovary or testis. Gonads play a double role: first, in producing and maturing gametes for reproduction, and, second, in secreting male and female hormones involved in the maturing of gametes and development of genital structures.

Gonadotropin: Any hormone having a stimulating effect on the gonads (ovaries or testes).

Gonadotropins, pituitary: Gonadotropic hormones secreted by the interior lobe of the pituitary gland: follicle-stimulating hormone, luteinizing hormone, and prolactin.

Gynaecomastia: Excessive development of the male mammary glands, even to the functional state.

Hormone: A chemical substance produced in the body by an organ or cells of an organ and transported through the blood to other organs or tissues on which it has a specific influence on various biochemical processes. Hormones are divided into three groups on the basis of their chemistry: steroid hormones (adrenal and genital), hormones derived from aromatic amino acids (adrenaline, thyroxine), and proteidic hormones (pancreatic, hypophyseal, and parathyroid).

Hormone, follicle-stimulating (FSH): One of the gonadotropic hormones of the interior pituitary, which stimulates the growth and maturation of graafian follicles in the ovary, as well as inducing the endometrial changes characteristic of the first portion of the mammalian menstrual cycle, and stimulates spermatogenesis in the male. FSH secretion is permanent in men, cyclical in women, but present during two phases (follicular and luteal) of the normal menstrual cycle. In general, FSH

stimulates the maturing and function of somatic cells associated with gametogenesis. FSH secretion is stimulated by luteinizing hormone releasing hormone.

Hormone, **inhibiting**: Hormones elaborated by one structure (as by the hypothalamus) that inhibit release of hormones from another structure (as from the interior pituitary gland).

Hormone, luteinizing (LH): A glycoprotein gonadotropic hormone of the interior pituitary, which acts with the follicle-stimulating hormone to cause ovulation in mature follicles and secretion of estrogen by luteal cells. LH secretion is permanent in men, cyclical in women with an increase at the end of the follicular phase, a pre-ovulatory peak, then a decline in the luteal phase. LH acts on many gonadal cells by promoting the synthesis of sexual steroids. In women, it is particularly active during ovulation.

Hormone, **releasing**: A hormone elaborated by one structure (as by the hypothalamus) that effects the release of hormones from another structure (as from the interior pituitary gland).

Hypogonadism: A condition resulting from or characterized by abnormally decreased functional activity of the gonads, with retardation of growth and sexual development.

Hypogonadism, **hypogonadotropic**: Hypogonadism due to failure of gonadotropin secretion as a result of understimulation by the hypothalamic-pituitary system.

Hypoplasia: Incomplete development or underdevelopment of an organ or tissue. **Hysterosalpingography:** Radiological examination of the uterine cavity and fallopian tubes after injection of an opaque material via the cervical canal.

Inhibition, **erectile**: Commonly called impotence: difficulty in achieving or inability to achieve erection in men.

Malignant: The quality of a condition that tends to become progressively worse and to result in death. Said of cancers.

Metabolism: The sum of all the physical and chemical processes by which living organized substance is produced and maintained (anabolism) and also the transformation by which energy is made available for the use of the organism (catabolism).

Metabolite: Any substance produced by metabolism or by a metabolic process.

Mucus: Clear, viscous, water-soluble substance normally secreted by the mucous glands and which protects the epithelial surfaces both mechanically and chemically. **Mucus, cervical:** Mucus produced by the cervix that undergoes complex changes in its physical properties in response to changing hormone levels during the reproductive cycle. These changes assist the survival and transport of sperm.

Muscle, **bulbospongiosus**: bulbocavernous muscle: central point of perineum stretched around the bulb and spongious tissue from the central fibrous core to the root of the penis. Comes into play in urination and erection.

Neurocrinia: Faculty of some neurons to elaborate a product of secretion that, by its passage in the blood and action on a target organ, has all the characteristics of a hormone.

Neurotransmitter: Chemical substance released in very small quantities from the axon terminal of a presynaptic neuron.

Oligospermia: A low concentration of spermatozoa in the sperm. A concentration of spermatozoa less than 20 million/mL is a factor in infertility.

Orchitis: Acute or chronic inflammation of the testicle usually associated with epididymitis.

Organ, accessory sexual: Structure for the transportation, protection, and nutrition of gametes and their removal from the gonads.

Ovulation: Rupture of an ovarian follicle that has reached maturity, accompanied by the discharge of an oocyte that is ready to unite with a spermatozoon.

Parasympathetic nervous system: The part of the autonomic nervous system that tends to induce secretion, to increase the tone and contractility of smooth muscle, and to cause dilation of blood vessels, and that consists of cranial and sacral parts. **Perineum:** The pelvic floor and associated structures occupying the pelvic outlet. In both men and women, the perineum can be divided into two triangles by a transversal line. The interior triangle including the external genital organs is called

the urogenital triangle, and the posterior triangle containing the anus, the anal triangle.

Pharmacokinetics: Study of the various stages of the metabolism of medications in the body (absorption, distribution, localization in tissues, biotransformation, and excretion) based on time and dose administered.

Placenta: A tissue formed when the embryo becomes implanted in the womb, allowing exchanges between fetus and mother and hormonal regulation during pregnancy. Fetal and maternal circulations come into contact in the placenta. The two are separated, however, by a placental barrier whose thickness varies from species to species.

Post-coital (test): Test for spermatozoa in the cervical mucus of the woman following sexual intercourse. The test permits the study of certain forms of male and female infertility (sperm count and motility, agglutination in the cervical mucus).

Progesterone: Hormone liberated by the corpus luteum, adrenal cortex, and placenta during pregnancy. The physiological role of progesterone is to prepare the uterus for the reception and development of the fertilized ovum and to promote its development. Progesterone is essential to sustaining pregnancy by its inhibiting action on uterine contractions. It is also secreted in smaller quantities by the testicles and adrenal cortex where it serves as an intermediary for biosynthesis of androgens and corticoids.

Prolactin: Hormone secreted by the interior pituitary gland. Its main role is the development and maintenance of milk production, but it also has numerous effects on reproduction, growth, and hydro-electric equilibrium. Many of these effects involve synergy with sexual steroids in target organs. Dopamine slows its secretion. **Pudendal nerve:** Rachidian nerve that originates in the sacral plexus, enters the pudendal canal, gives off the inferior rectal nerve, and then divides into the perineal nerve and dorsal nerve of the external genital organs.

Receptor: Specialized type of cell that transforms physical or electrophysiological stimuli into slow, graduated potential actions.

Scrotum: The pouch that contains the testes and their accessory organs.

Sperm: Opaque, white, flocculent liquid produced by ejaculation and composed of spermatozoa in suspension in seminal fluid (mixture of secretions from the various male genital glands).

Spermatid: A germinal cell derived from a secondary spermatocyte by fission, and developing into a spermatozoon.

Spermatogenesis: The set of processes that result in the formation of male gametes within the epithelium of the seminiferous tubules.

Sympatholytic: Any substance that inhibits the effects of sympathetic stimulation at various levels.

Synapse: The site of functional apposition between neurons, at which an impulse is transmitted from one neuron to another by electrical or chemical means. The nerve cell that sends the impulse is the presynaptic cell, the cell that receives the impulse the postsynaptic.

Syndrome, parkinsonian: A syndrome associated to varying degrees with slow involuntary tremor, limited movement, and muscle rigidity.

Tachycardia: Permanent acceleration of the heart rate beyond 100 beats per minute.

Tachyphylaxis: Rapidly decreasing response to a drug or physiologically active agent after administration of a few doses. The effect of the substance may disappear after a few minutes in the course of repeated injections. This acute tolerance differs from the most general form, which is the gradual disappearance of the effects of the substance with repeated administration of identical doses.

Terminal, **axon**: Set of ramifications located at the distal part of the axon, in synaptic contact with another nerve cell, muscle fibre, or glandular cell.

Tolerance: Gradually acquired resistance to certain toxic substances. Tolerance implies the ability to tolerate increasing doses of such substances to obtain the same effects, the person remaining sensitive to a relative excess. If administration of the substance is discontinued for a certain time, there is usually a return to the initial degree of sensitivity.

Varicocele: Enlarged or damaged veins in the testicles or vas deferens; a major cause of infertility in men.

Vas deferens: The duct that carries sperm from the testis to the ejaculatory duct to the penis.

Vesicle, seminal: Membranous reservoir located below the base of the prostate within the vas deferens in which sperm accumulates between ejaculations.

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A Literature Review of the Physiological Manifestations Related to Infertility Linked to Weight, Eating Behaviours, and Exercise

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Executive Summary

A literature review was prepared for the Royal Commission on New Reproductive Technologies. The objective was to document physiological links to infertility associated with weight, eating behaviours, and exercise. Available clinical and research data were reviewed according to four areas of interest: eating behaviours, exercise, nutrition, and obesity. An inadequate ratio of body fat to body weight caused by loss of weight or maintenance of weight at suboptimal levels appeared to be a critical etiological factor linked to infertility in women who exercised excessively, used dietary restriction to maintain lower than expected weight for height, or presented with an eating disorder. Weight per se was also critical in obesity-related infertility. Loss of weight was found to be effective in restoring normal reproductive functioning in infertile obese women. The physiological mechanisms underlying infertility associated with weight, eating behaviours, and exercise were unclear, although a disturbance in the hypothalamic-pituitary axis was suspected. Very little research was found with regard to male infertility. Undernutrition and obesity in men appeared to be associated with mild reproductive dysfunction. Future infertility research will need to account

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for the interrelationships among the biopsychosocial factors involved in eating behaviours, exercise, and weight.

Introduction

Weight, eating behaviours, and exercise are believed to be etiological factors contributing to infertility because of their impact on the reproductive functioning of both men and women. The aim of this report was to document physiological links to infertility that were indicated from available clinical and research data, in order to provide a basis for further study.

Methodology

A literature search was conducted using MEDLINE and PsychINFO data bases as initial resources to obtain relevant medical, psychosomatic, psychiatric, sociological, and psychological literature. Parameters of this search included accessing reports published from 1980 to 1991, in both English and French, with regard to female and male infertility linked to weight, eating behaviours, and exercise. To be consistent with the Royal Commission on New Reproductive Technologies, infertility was defined as difficulty conceiving, the inability to conceive, or the inability to carry a pregnancy to term.

The literature review was organized according to the following areas of interest: (1) eating behaviours, including psychiatric diagnoses of anorexia nervosa (AN) and bulimia nervosa (BN) as well as subclinical eating disorders and practices of weight control; (2) exercise; (3) nutrition; and (4) obesity. Literature was critically evaluated for each of these areas of interest with respect to proposed etiological links to infertility and the physiological evidence supporting or refuting these links. Evidence indicating the long- and short-term duration and/or the reversibility of infertility associated with eating behaviours, exercise, nutrition, and obesity was described where available, and prevalence or incidence data were reported.

Summary charts were prepared for each of the four areas of interest (see Appendices 1 to 4). Each chart presents the articles reviewed according to the following methodological properties: type of study, definitions of diagnostic criteria, measures of sample size, etiological links to infertility, and conclusions concerning fertility status.

Few references were obtained that were pertinent to the fertility status of men. In addition, although both English and French language references were searched, no relevant French language publications concerning male fertility status were accessed. Consequently, the following review refers to the fertility status of women, unless otherwise stated.

Literature Review

Eating Disorders

Anorexia Nervosa

AN was characterized by self-imposed starvation as a result of a relentless pursuit of thinness and a morbid fear of fatness. Although not entirely a twentieth-century phenomenon, changes in attitudes in Western society, including a generalized preoccupation with the concept that success and happiness are tied to thinness, have increased the prevalence of the problem. Estimates indicated that 1 percent of young adult women suffered from AN (Garfinkel and Garner 1982). Diagnostic criteria included weight loss and maintenance of body weight 15 percent below expected, an intense fear of weight gain, body image disturbance, and the presence of primary or secondary amenorrhoea (American Psychiatric Association 1987; see Appendix 5).

Infertility Associated with Anorexia Nervosa

Physiological Links

Primary and secondary amenorrhoea (absence of menstruation) were important diagnostic markers for AN. Several reviews (Garfinkel and Garner 1984; Bates 1985; Reid and Van Vugt 1987; Frisch 1990) indicated that amenorrhoea associated with this eating disorder was caused by hypothalamic dysfunction.

The underlying physiological mechanisms of anorexic amenorrhoea were thought to be complex and not solely attributable to the occurrence of simple weight loss. A combination of physical, psychological, and nutritional stressors influenced fertility status in women with AN.

The physiological changes occurring in AN appeared to represent a regression to pre-pubertal functioning. Evidence suggested that an abrupt or marked weight loss together with physical or psychological stress disrupted gonadotropin-releasing hormone (Gn-RH) production from the hypothalamus leading to endocrine abnormalities such as luteal-phase defects, which in turn resulted in oligomenorrhoea or amenorrhoea. Specifically, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol (E_2) decreased to secretory patterns similar to those found in pre-pubertal girls (Reid and Van Vugt 1987; Frisch 1990). Important factors in understanding the hypothalamic dysfunction associated with AN included the fact that it was the loss of percentage of body fat rather than body weight per se that was crucial (Frisch 1990). Loss of 15 percent body weight was equivalent to the loss of 33 percent body fat (Bates 1985). It

was suggested that a weight loss to below 85 percent ideal body weight represented anovulatory cycles, a weight loss to between 85 and 95 percent ideal body weight represented a luteal-phase defect, and weight at or above 95 percent ideal body weight represented normal menstrual/reproductive functioning (Bates and Whitworth 1982). In general, weight restoration in AN was found to signal a return of normal menses and the gonadotropin secretory pattern was thought to mimic puberty (Bates 1985; Treasure et al. 1985).

Recent research findings supported the data described in the review articles. Measurement of menstrual functioning and gonadotropin levels in samples of women meeting diagnostic criteria for AN revealed serum LH and FSH levels that were low but within normal limits (Bates and Whitworth 1982; Wentz 1980). Even small changes in body weight (5 to 10 percent) were associated with subtle alterations in menstrual cycle that led to reproductive failure (Bates 1985).

Prevalence of Anorexia Nervosa in Infertile Women

The prevalence of eating disorders in infertile women was investigated. Increasing evidence suggested that eating disorders (AN and BN) accounted for a significant proportion of women referred for treatment of unexplained infertility (Bates 1985). A recent study found a 7 percent prevalence rate of diagnosable (DSM-III-R) eating disorders in Canadian women who were attending an infertility clinic. This rate was two to four times greater than the prevalence of eating disorders predicted for a population of women attending a general practice (King 1989). The prevalence rate increased to over 16 percent when subclinical eating disorders were included (Stewart et al. 1990). The authors proposed that women attending infertility clinics should be screened for eating disorders before other investigations or treatment of infertility are pursued.

Pregnancy and Anorexia Nervosa

The effect of AN on the course and outcome of pregnancy was associated with risk factors such as low infant birthweight, complications of labour and delivery, and infant perinatal mortality and morbidity (Van Wezel-Meijler and Wit 1989; Abraham et al. 1990; Stewart et al. 1987; Treasure and Russell 1988; Brinch et al. 1988). A Canadian study reported the pregnancy rate and the health of their infants for a sample of 74 women who had been treated for AN (Stewart et al. 1987). Fifteen of the women conceived 23 pregnancies. Some infertility problems were identified in the remaining 59 women, but single status and young age largely accounted for their relatively low conception rate. Among those who conceived, all complications of pregnancy and delivery occurred in women who were ill with AN at the time of conception. There was one fetal intrauterine death at 15 weeks' gestation; two women had Caesarian sections and their infants had low Apgar scores and neonatal problems such as respiratory distress

and jaundice. In comparison, women in remission from AN were found to have healthier babies with higher Apgar scores.

Risks to the intrauterine growth of their infants were reported for women who conceived while at suboptimal weight as a result of AN (Treasure and Russell 1988). These women were found to gain less weight (8 kg) than the norm for pregnant women without eating disorders (11 kg). Serial ultrasonography indicated that the rate of fetal growth was diminished during the last trimester. However, the infants were observed to have a period of "catch up" growth after birth, and they were healthy and within the expected norms at six months of age.

The risks of having low-birthweight infants and perinatal mortality were further substantiated in studies of women who became pregnant while recovering from an eating disorder and who were still at low body weight. Increased risk of low birthweight and neonatal mortality were reported (Abraham et al. 1990; Treasure and Russell 1988; Van Wezel-Meijler and Wit 1989). A Scandinavian follow-up study of the reproductive pattern in women previously treated for AN found the rate of prematurity to be twice that expected and the perinatal mortality to be six times that expected in the general population. The fertility rate was one-third that expected in the population at large (Brinch et al. 1988).

Summary of Infertility and Anorexia Nervosa

Infertility associated with AN appeared to be caused by hypothalamic dysfunction that led to amenorrhoea. Loss of weight and percentage of body fat were critical etiological factors. Infertility resulting from anorexic amenorrhoea was reversible upon weight restoration. The capacity to carry a pregnancy to term appeared to be significantly compromised in women who maintained suboptimal weights. Premature births, stunted intrauterine growth, low birthweight, and perinatal mortality above that expected on the basis of norms for the general population were reported. More recent studies recommended screening for eating disorders, excessive weight concerns, and weight maintenance at suboptimal levels when women present for treatment of infertility. Treatment of any underlying eating disorder or weight concern was recommended prior to hormonal correction of infertility.

Bulimia Nervosa

BN was a more recently described eating disorder (Russell 1979) involving recurrent episodes of the rapid consumption of large amounts of food and purging behaviours in the context of persistent preoccupation with weight and shape (American Psychiatric Association 1987; see Appendix 6).

Infertility Associated with Bulimia Nervosa

Physiological Links

Fewer studies describing the reproductive function of women with BN were available than for AN. Menstrual disturbances were common in bulimic women (50 percent), with inadequate luteal phase, oligo-

menorrhoea, and amenorrhoea frequently observed (Copeland and Herzog 1987; Pirke et al. 1987). Etiological links between BN and infertility were assumed to be similar to those found in AN, but one important difference between the two eating disorders was that bulimic women were not obviously underweight or as starved as anorexic women. Contributory factors such as weight loss, inadequate nutrition, chaotic eating behaviours including binging and purging, and psychological distress were thought to present considerable challenges to the reproductive physiology in women with BN. It was suggested that for bulimics who have normal weight the disruption of gonadotropin secretion was not as profound as that found in AN. It was hypothesized that the crucial reproductive disturbance originated in the hypothalamus, specifically that gonadotropin secretion decreased and Gn-RH secretion was disrupted.

Recent research evidence, however, suggested a higher prevalence of menstrual disturbance in women with BN than previously thought (Pirke et al. 1987, 1988). In one study, analysis of hormones of 15 women who were bulimic indicated that variability of reproductive dysfunction existed (Pirke et al. 1987). Half of the women were found to have impaired follicular development, low estradiol levels, and significantly lower weight than the other women in the sample. The authors suggested that low body weight was the most important contributory factor to the reproductive hormone impairment in these bulimic women. Intermittent dieting and highly abnormal eating behaviours were additional potentially disruptive factors. A later study (Pirke et al. 1988) reported that impaired gonadotropin secretion caused the reproductive dysfunction.

The relationship between BN and polycystic ovary syndrome (PCOS), a condition associated with menstrual irregularities, hirsutism, obesity, and infertility, was also investigated (McCluskey et al. 1991). Of women diagnosed with PCOS, one-third reported abnormal eating behaviours suggestive of a diagnosis of BN. As a result, the authors recommended routine screening for BN in women who were diagnosed to have PCOS.

Pregnancy and Bulimia Nervosa

The course and outcome of pregnancy for women with BN were not studied sufficiently. Evidence that bulimic anorexics were at risk for low-birthweight infants and pre-term delivery was reported (Stewart et al. 1987); however, a recent study of four primiparous bulimic women (Willis and Rand 1988) revealed that pregnancy outcome was not adversely affected by BN.

Summary of Infertility and Bulimia Nervosa

Few data were available concerning the reproductive capacity of women diagnosed with BN. To date, no long-term follow-up studies evaluating fertility rates in bulimic women had been published, perhaps because of the recent evolvement of this eating disorder. However, the available research indicated that reproductive dysfunction was apparent in women with BN. A higher rate of menstrual disturbance than previously

suspected and some evidence to support a hypothalamic dysfunction were reported recently. In addition, it was speculated that the reproductive dysfunction in some women with BN may have been masked by the so-called "normal" weight of women suffering from this eating disorder. Significant weight fluctuations also occurred with BN, as well as severe nutritional disturbance, but future research was required to substantiate the hypothesized hypothalamic etiological links of the reproductive dysfunction and also the reversibility of infertility in BN.

Subclinical Eating Disorders and Weight Control

Subclinical eating disorders and weight control studies concerned women who manifested eating disorders not meeting full DSM-III-R diagnostic criteria for AN or BN (American Psychiatric Association 1987; see Appendices 5 and 6) and women who were weight preoccupied or dieting to maintain a low body weight. The pervasive societal preoccupation with thinness has led to the nearly universal adoption of restrictive eating behaviours by Western women. Bates (1985), in his review of weight control and infertility, asserted that the present-day preoccupation with thinness accounted for a significant proportion of women with unexplained fertility. Many women who maintained suboptimal weights for their height, without exhibiting overt symptoms of an eating disorder, did present for investigations of infertility (Bates 1985; Stewart et al. 1990). Weight preoccupation in infertile women was investigated in one study (Allison et al. 1988) in which women with anovular cycles were found to be significantly more concerned with dieting and fearful of weight gain than infertile women with ovulatory cycles.

Exercise

No consistent definition of exercise was obtained as a result of the literature search. However, most publications acknowledged that during the past two decades increasing numbers of women had begun to exercise regularly, coinciding with the surge of interest in fitness. Descriptive definitions such as strenuous, rigorous, and aerobic exercise were generally used with reference to the examination of exercise and its association with reproductive dysfunction and infertility.

Infertility Associated with Exercise

Physiological Links

A number of review articles summarized the currently understood association between infertility and exercise (Cumming 1991; Highet 1989; Loucks 1986; Meeks 1986; Cumming and Rebar 1983; Baker 1981). Strenuous exercise was found to result in various forms of menstrual dysfunction, including delayed menarche, altered pubertal progression, defective luteal phase, anovulation, amenorrhoea, and infertility (see, for example, Warren 1983; Highet 1989). The etiological mechanisms for the disturbances in reproductive function were thought to originate in the

hypothalamic-pituitary axis. Levels of the reproductive hormones—estrogen, progesterone, LH, and, to a lesser extent, FSH—were reduced in exercise-induced menstrual disturbance. Increases in prolactin, growth hormone, testosterone, adrenocorticotropic hormone, adrenal steroids, and endogenous opiates were also postulated to play an etiological role in athletic amenorrhoea (Highet 1989; Reid and Van Vugt 1987; Cumming 1991).

The etiology of exercise-related infertility was further complicated by an array of modulating factors. Amount of body fat, training intensity, age, type of exercise, nutrition, stress, and eating disorders were thought to be important influences in the complex interplay among reproductive mechanisms. In particular, the critical fat hypothesis (Frisch 1990) and the energy drain hypothesis (Warren 1983) received considerable attention in the research. The critical fat hypothesis suggested that a threshold weight for height, indicated by a critical percentage of fat, was necessary for ovulatory menstrual cycles. The concept of energy drain postulated that intensive training involved in activities such as running, ballet, and gymnastics together with low body fat caused an increased metabolic rate that influenced hypothalamic function and led to amenorrhoea.

Epidemiological estimates of the incidence of athletic infertility ranged widely, from 1 to 50 percent (Baker 1981). To date, an accurate estimate of exercise-induced infertility is not available. Recent findings suggested that the incidence of infertility among athletes might be much greater than indicated by reported rates of amenorrhoea. For example, menstruating athletes were found to have anovulatory cycles (Highet 1989; Prior 1982).

Much of the literature reviewed questioned the validity of earlier research concerning the relationship between exercise and infertility (Loucks 1986). Inappropriate extrapolation of animal data, statistical analyses, and physiological measures, as well as small sample sizes, were major impediments to the interpretation of pre-1980 research findings.

Recent research evidence indicated that exercise may be best understood as an often subtle stressor rather than a direct component of the physiopathology of infertility. One controlled study of 326 infertile women with ovulatory failure found no association between infertility and ovulatory dysfunction in women who exercised less than 60 minutes a day. Identified risk factors were nulliparity and vigorous exercise, defined as aerobic activities that required 0.01 kcal/min per day to perform activities such as running, aerobic dancing, tennis, and downhill skiing. Women who had not been pregnant before and who had engaged in vigorous exercise for 60 minutes or more a day were at risk for developing infertility (Green et al. 1986). A study of the hormonal effects of a moderate training program on a sample of seven college women (Bullen et al. 1984) found that overt cyclicity was unimpaired — plasma reproductive hormones showed insignificant acute changes. Decreased secretion of estriol and progesterone was observed in four women in this study, indicating a disturbance in their ovarian function. The authors speculated that the

ability to conceive may have been impaired in these women because of disturbances in steroid secretion (ibid.). Parity and age were found to be risk factors for infertility. The incidence of secondary amenorrhoea was reported to be higher in nulliparous women 30 years of age or younger (Baker et al. 1981). Nutritional status was also proposed as a risk for developing athletic amenorrhoea. Specifically, vegetarianism was thought to be associated with a higher incidence of secondary amenorrhoea (Brooks et al. 1984).

Exercise, Eating Disorders, and Weight Control

Excessive exercise was a frequently used method of weight control in both AN and BN, and many women who engaged in athletics or heavy endurance training, such as ballet, had eating disorders or subclinical signs of an eating disturbance. Important interrelationships between intensity of exercise, nature of eating behaviours, and methods of weight control existed and needed to be considered in discussions of etiological associations of exercise to infertility (Mansfield and Emans 1989; Reid and Van Vugt 1987; Frisch 1990).

Exercise and Pregnancy

Exercise has been considered to have a negative impact on the course and outcome of pregnancy. Assumed risks included fetal hypoxia, hyperthermia leading to teratogenesis, miscarriage, premature rupture of membranes, placental abruption, premature labour, and long-term fetal hypoxia (Snyder 1990), but little conclusive evidence existed to establish clear etiological links of exercise as a risk factor in pregnancy (Snyder 1990; Jarski and Trippett 1990; Huch and Erkkola 1990; Fishbein and Phillips 1990; McMurray and Katz 1990).

Few negative effects of exercise during pregnancy were identified, and they were, in general, outweighed by the potential benefits (Beckmann and Beckmann 1990; Durak et al. 1990). Moderate exercise and exercise in water were recommended as the safest (Pivarnik et al. 1990; Durak et al. 1990; Sady et al. 1990; Katz et al. 1990a; Clapp 1990; Hume et al. 1990; Watson et al. 1991; McMurray and Katz 1990).

Negative influences of exercise during pregnancy were reported from investigations of women serving in the U.S. military. Increased odds of preterm delivery and ectopic pregnancy were found in women who were engaged in the physical training required for the military (Ramirez et al. 1990; James 1990). Intense exercise in later stages of pregnancy was observed to limit fetal growth. Significant differences in birthweight and percentiles of birthweight were found when aerobic dancers and recreational runners were compared (Clapp and Capeless 1990); the aerobic dancers had smaller infants.

A prospective study of the effects of exercise on pregnancy found that long periods of standing were associated with a moderately increased risk of pre-term delivery (Klebanoff et al. 1990). Women who engaged in these activities were found in general to qualify for lower socioeconomic status

than women who were engaged in heavier work activities. It was concluded that unmeasured differences of socioeconomic status may have been important confounding variables in existing research.

A current research focus was to investigate the mechanisms and physiological properties of exercise. Data from this research provided further elucidation of the hormonal changes associated with a variety of aerobic activities and may in the future substantiate etiological links with reproductive dysfunction currently proposed (Carpenter et al. 1990; McMurray et al. 1990; Ruissen et al. 1990; Van Raaij et al. 1990; Katz et al. 1990b).

Summary of Exercise-Related Infertility

Despite the burgeoning literature that examined the effects of exercise on the status of women's fertility, the precise role of exercise remained unclear because of the complexity of interrelated factors such as weight control, nutrition, and eating behaviours. Reproductive dysfunction associated with exercise was found to be reversible when changes in lifestyle were made. These changes included decreasing the intensity of training and improving nutrition, and frequently involved weight gain. Current understanding of the effect of exercise on fertility status suggests that the benefits outweighed the risks.

Nutrition

Undernutrition in Western society frequently occurred as a result of self-imposed dietary restriction. This was in contrast to developing countries, where malnutrition is the result of food shortage and famine (Van Der Spuy 1985). Links between undernutrition and infertility were examined.

Undernutrition and Infertility

Undernutrition was a contributory factor of amenorrhoea associated with eating disorders, exercise, dietary restriction, and weight loss (Warren 1983). A disturbance of the hypothalamic-pituitary axis was thought to be the underlying mechanism causing amenorrhoea (see sections on eating disorders and exercise). Other endocrine abnormalities such as alterations in thyroid function, plasma growth hormone, and insulin secretion were identified with respect to reproductive dysfunction and undernutrition (Warren 1983; Van Der Spuy 1985).

Dietary restriction affected infertility status. Van Der Spuy (1985), in her review, stated that women who maintained suboptimal weights prior to pregnancy and had poor pregnancy weight gain were at risk for fetal intrauterine stunting and delivery of low-birthweight infants, with consequent increased perinatal morbidity and mortality (Landon et al. 1986).

Vegetarianism was increasingly associated with society's general preoccupation with weight loss and dieting. Moreover, vegetarianism was

frequently the diet of choice for women athletes and women with eating disorders. Recent evidence indicates that type of diet, in particular vegetarian diet, was associated with a higher frequency of anovulation and infertility in women (Pirke et al. 1986; Brooks et al. 1984). In one study, the effects of weight loss in 18 healthy women who were assigned randomly to vegetarian or non-vegetarian diets revealed that 7 out of 9 women in the vegetarian group became anovulatory as a result of the diet, whereas 7 of the 9 non-vegetarian women maintained ovulatory cycles.

Undernutrition and Lactation Infertility

Comparisons between Western women and women from developing countries were among the studies that linked post-partum lactation infertility with nutritional status (Lunn et al. 1980, 1984; Shatrugna et al. 1982). Hyperprolactinaemia without involvement of other hormones was associated with infertility caused by breast feeding. Lower prolactin levels were found in Western women when compared with women from developing countries. A shorter duration of lactation infertility was also found in Western women and was attributed to their generally improved nutritional status (Huffman 1983; Lunn et al. 1980).

Male Infertility and Undernutrition

Limited information with regard to undernutrition and male infertility was found in the literature. One study of gonadal function in men with celiac disease (Farthing et al. 1982) indicated that infertility and sexual dysfunction in these men may have been associated with nutritional deficiency. In another study, reduction of general nutritional status was thought to contribute to the impaired semen quality found in men with Crohn's disease (Farthing and Dawson 1983).

Summary of Undernutrition and Infertility

Nutritional status was part of the complex array of hormonal events influencing reproductive function. Undernutrition was best understood as a vulnerability factor in the etiology of infertility. Western women who practised dietary restriction, sometimes to the extreme of self-imposed starvation, were more vulnerable to infertility. Reproductive dysfunction as a consequence of undernutrition was normally reversible once adequate nutrition and normal body composition in terms of lean to fat ratio were restored (Van Der Spuy 1985).

Obesity

Obesity was defined as body weight 20 percent above the upper limit for height, or body fat 30 percent or more in females and 25 percent or more in males. Another definition of obesity was based on body mass index (weight/height²). A body mass index above 30 kg/m^2 signalled obesity (Bray 1986).

Obesity and Infertility

Physiological Links

Research indicated that obesity was a causal factor in anovulation, although most obese women and men were fertile (Friedman and Kim 1985; Reid and Van Vugt 1987; Whitaker 1987). The severity of reproductive dysfunction associated with obesity was found to increase with increasing percentage of weight over ideal body weight (Friedman and Kim 1985). No clear understanding of the etiological role of obesity and infertility was described. Obesity was most frequently associated with hyperandrogenism, which was thought to contribute to anovulation and inadequate luteal phase (Friedman and Kim 1985; Whitaker 1987). The ovary was thought to be the major source of the androgen excess. Increased estrogen and an abnormal LH/FSH ratio were also associated with obesity-induced infertility. Obesity-related anovulation was frequently discussed in association with PCOS, although this connection was still controversial (ibid.).

Evidence regarding the hormonal mechanisms of obesity confirmed the association between obesity and menstrual cycle disturbance and infertility. Kusakari et al. (1990) found an increased tendency toward obesity in infertile women with ovulatory dysfunction. Kopelman et al. (1980), in a study of plasma concentrations of sex steroids and sex hormone binding globulin (SHBG) in massively obese women, found abnormal secretion and binding of these hormones and attributed these hormonal changes to obesity.

Obesity was thought to negatively influence the course of pregnancy because of the risks of maternal hypertension and large-for-gestational-age infants. Few studies, however, demonstrated an increase in neonatal or maternal mortality as a consequence of obesity (Friedman and Kim 1985; Gross et al. 1980).

One study (Bohrer and Kemmann 1987) identified obesity and age as risk factors for spontaneous abortion in previously infertile women treated with menotropin. Women who weighed more than 81 kilograms and were 35 years of age or older were found to have a significantly higher chance of miscarriage.

Obesity, Weight Reduction, and Infertility

Most of the literature reviewed indicated obesity-related infertility or menstrual disturbance to be normalized upon weight reduction (Bates et al. 1982; Kim et al. 1982; Deital et al. 1988). Bates and Whitworth (1982) found that simple weight loss reduced androgen excess in obese infertile women and restored cyclic ovulation in 85 percent of women who had lost 15 percent of their body weight. Weight loss by surgical means was studied in massively obese women. One retrospective review of the outcome of bariatric surgery (jejunoileal bypass) performed on 138 Canadian women revealed a pre-surgery incidence of infertility of 29 percent. Those women who tried to conceive post-surgery (mean weight loss ≥ percent excess

weight) were successful, and no obstetric complications were noted after weight loss stabilization. Kim et al. (1982), however, did not find a return of ovulatory function after studying gastric stapling for weight loss in morbidly obese women who were oligomenorrhoeic. The women in this study remained obese after treatment, and the authors suggested that these women may have required more weight loss prior to the resumption of normal menstruation. Printen and Scott (1982) reported on the pregnancy risks on morbidly obese women of post-gastric bypass surgery. Apart from a period of rapid weight loss and an immediate post-operative period when metabolic and nutritional stabilization occurred, pregnancy was found to be well tolerated, with no overt maternal or fetal risks.

Obesity and Male Infertility

Very little attention was paid to infertility and obesity in men. One study evaluated the pituitary-gonadal axis and found a state of mild hypogonadotropic hypogonadism for obese men, as shown by plasma concentrations of sex steroids (Strain et al. 1982). Another study measuring serum estradiol in infertile men found no relationship with lower estrogen and obesity (Hargreave et al. 1988). The effect of weight loss on reproductive hormones was investigated in a study of morbidly obese men (Stanik et al. 1981). Weight loss of more than 19 kilograms was reported to be associated with the normalization of circulating estrogens and androgen binding.

Summary of Obesity and Infertility

Inconsistent definitions of obesity were found in the literature. Overall, most obese men and women were fertile. No clear etiological role for obesity in infertility was established, though hyperandrogenism was associated with anovulation. Studies revealed that normal reproductive function resumed after weight reduction. Some indication that massively obese women (75 to 100 percent above expected weight for height) responded less well to weight loss treatments. Data concerning fertility status of obese men suggested mild reproductive disturbance that was reversed with weight loss.

Conclusions

A complex interplay of biopsychosocial factors appeared to influence the fertility of women who presented with eating disorders, who exercised, or who used dietary restriction as a method of weight control. Weight and percentage of body fat appeared to be critical factors that influenced reproductive functioning. A precise understanding of the physiological links was still unclear, though the majority of evidence suggested a disturbance in the hypothalamic-pituitary axis.

The prevalence of eating disorders, particularly AN, was found to be higher for infertile women than for the general population, hence supporting recommendations to screen women for eating disorders and dietary restriction practices who present for treatment of infertility. With regard to exercise, the prevailing evidence suggested that the beneficial effects of exercise outweighed the risks of infertility. Negative effects of exercise were largely related to intense physical training used in activities such as aerobic dancing or in the military. Undernutrition as a result of chronic dietary restriction, common in the general population of Western women, was best understood as a vulnerability factor in the etiology of infertility.

There was substantial evidence to indicate that infertility associated with abnormal eating behaviours, excessive exercise, and undernutrition

Author(s)	Type of study	Diagnostic criteria definition	
Stewart et al. (1990)	Prospective screening for prevalence of disorders in infertile women	DSM-III-R eating disorder; ide body weight (life insurance an society of actuaries)	
Bates (1985)	Review of weight control as a cause of infertility		
Bates et al. (1982)	Investigation of effects of weight control and weight gain in infertile women	Ideal body weight (Metropolita Life Insurance tables)	
Allison et al. (1988)	Investigation of weight, eating patterns, and psychological disturbance as risk factors for infertility	Ideal body weight (U.S. Societ of Actuaries)	
King (1989)	Investigation of prevalence and clinical profile of eating disorders in general-practice populations in U.K.	Russell's (1979) criteria; eating attitudes test; clinical interview schedule; eating interview	

was reversible with improved nutrition, weight gain, and a decrease in the level of exercise. Similarly, infertility associated with obesity was reversed with weight loss.

In general, very few published data were found with regard to male infertility associated with eating behaviours, exercise, nutrition, and obesity. Indications of mild reproductive disturbance have been reported for men who were obese or who suffered from undernutrition as a result of disorders such as Crohn's disease or celiac disease.

Future research will need to take into account the multivariate nature of physiological, psychological, environmental, and social influences on the fertility status of women and men in terms of eating behaviours, exercise training, and weight control.

nple size Isures	Etiological links to infertility	Conclusions re fertility status
66 infertile women; ng attitudes test - 26	Prevalence of eating disorders (16%)	Eating disorders had an important etiological role in infertility
	Women with "ideal" slim habitus had high incidence of unexplained infertility	Fascination with slimness may have been cause of unexplained infertility
47 infertile women; ght, blood samples: FSH ratio	As body weight increased normal LH/FSH ratio was restored; women began to conceive at >95% of their predicted ideal body weight	Infertility was linked secondarily to weight control practices; normal menstrual cycles resumed upon weight correction
38 infertile women; ng disorder inventory, eral health questionnaire, um assays, basal body perature	Women with anovulatory cycles were more concerned with dieting and weight and had a greater fear of fatness than ovulatory infertile women	A significant proportion of women attending infertility clinics were preoccupied with weight
.720		1% of women aged 16-35 years had BN; 3% of women had partial syndrome eating disorder

Appendix 1. (cont'd)

Author(s)	Type of study	Diagnostic criteria definition
Stewart et al. (1987)	Investigation of course and outcome of pregnancy for women previously treated for eating disorder	
Reid and Van Vugt (1987)	Review of endocrine changes associated with weight loss, exercise, obesity, and reproductive function	
Abraham et al. (1990)	Investigation of eating and exercise behaviours in women with 2° amenorrhoea	2° amenorrhoea: hypothalami (n = 10); hypogonadotropic post-pill (n = 4); DSM-III eating disorder
Garfinkel and Garner (1984)	Review of menstrual disorders and AN	
Treasure and Russell 1988)	Case study of pregnancy outcome in AN	
Wentz (1980)	Investigation of role of body weight and weight loss in amenorrhoea	Metropolitan Life height and weight tables

Author(s)	Type of study	Diagnostic criteria definition
Brinch et al. (1988)	Follow-up of reproductive outcome in AN	
McCluskey et al. (1991)	Investigation to establish relationship between PCOS and bulimia	DSM-III, BITE Questionnaire, PCOS: ultrasound
Pirke et al. (1988)	Investigation of menstrual cycle in BN	DSM-III, body mass index
Pirke et al. (1987)	Investigation of plasma concentrations of ovarian hormones in BN	DSM-III (1980)
Willis and Rand (1988)	Case study to describe pregnancy in bulimic women	DSM-III (1980)
Copeland and Herzog 1987)	Review of menstrual abnormality and BN	

mple size asures	Etiological links to infertility	Conclusions re fertility status
: 15 women who had en birth; interviews	10% infertility problems (general population: 10% infertility), mothers with active anorexia; perinatal mortality 6x expected; 14.3% of infants born <2 500 g (general population 6.8%)	Offspring of mothers with AN: high risk for infant undernutrition and stunting
= 375 women; ultrasound, dy mass index, endocrine says	One-third of the women with PCOS 6x more likely to have abnormal eating behaviours (binge/fasting); they were 2x more likely to have subclinical bulimia	Clear association between abnormal eating behaviours and PCOS; need to screen women with PCOS for bulimia
= 15 women with bulimia, = 9 controls; weight rmone assays	Menstrual dysfunction in bulimic women more severe; no follicular development; inadequate luteal phase	Low body weight most important factor impairing follicular development in bulimia
= 15 women with bulimia, = 10 controls	Only 1 BN patient had normal menses; 7 patients amenorrhoea/oligo- menorrhoea; 7 patients short luteal phase	More bulimic patients had disturbed menstrual cycles than expected; eating habits were implicated as possible etiological factors
= 4 primiparous bulimic omen; interview, infant rthweight, gestational age, aternal weight gain	Pregnancy outcome was not adversely affected by bulimia	Fertility rates in bulimia were unknown
	Menstrual disturbances common in bulimic women (amenorrhoea/oligo- menorrhoea)	AN model a basis for understanding reproductive function for BN

Author(s)	Type of study	Diagnostic criteria definition
Van Wezel-Meijler and Wit (1989)	Case study of offspring of mothers with AN	
Treasure et al. (1985)	Investigation of persistent menstrual dysfunction in AN	Russell's criteria for AN
Frisch (1990)	Review of weight and reproductive function	

nple size asures	Etiological links to infertility	Conclusions re fertility status
2 women with AN	Case #1 gonadotropic hormone-induced ovulation, pregnancy 34 weeks, twins low birthweight; Case #2 clomiphene-induced pregnancy, low-birthweight infant	Mothers with AN presented with high risk for undernutrition and slow growth of infants
: 30 women with AN; rasound	Ovaries of anorexic women were smaller than normal; ovarian volume increased with weight gain	Regression of hypothalamic pituitary-gonadal function in AN to pre-pubertal stage
		Weight loss 10%-15% ideal body weight had 1° or 2° amenorrhoea; amenorrhoea was reversible with weight gain

Appendix 2. Summary of Literature Review: Exercise

Author(s)	Type of study	Criteria definitions
Highet (1989)	Review of athletic amenorrhoea	
Green et al. (1986)	Investigation of exercise as a risk factor for infertility	Infertility: women who did no conceive despite trying for the year; ovulatory abnormality: oligomenorrhoea, amenorrhoeabnormal body temperature
Loucks (1986)	Review of effect of exercise on reproductive hormones in women	
Prior (1982)	Review of hormonal and hypothalamic changes with endurance training	
Clapp and Capeless (1990)	Investigation of regular running/aerobics during late pregnancy >50% preconceptual levels on fetal growth	Well-conditioned recreational athletes
McMurray et al. (1990)	Investigation of effect of pregnancy on plasma beta- endorphin response to exercise in water	<i>د</i> ٠
Van Raaij et al. (1990)	Longitudinal study of energy cost in pregnancy	= 71

Type of study	Criteria definitions
Review of menstrual dysfunction and hormonal status in athletic women	Menstrual dysfunction: amenorrhoea, oligomenorrho
Investigation of female runners and 2° amenorrhoea	
Investigation of effects of exercise on reproductive function in girls	
Investigation of aerobic exercise on land vs. water in pregnancy	
Investigation of physical activity and pregnancy outcome in a prospective cohort	Onset of labour: regular uter contractions, progressive cervical change; pre-term labour: <37.5 weeks' gestatio
Investigation of impact of aerobic exercise on course and outcome of pregnancy	1 a
Prospective study of exercise and pregnancy	
	Review of menstrual dysfunction and hormonal status in athletic women Investigation of female runners and 2° amenorrhoea Investigation of effects of exercise on reproductive function in girls Investigation of aerobic exercise on land vs. water in pregnancy Investigation of physical activity and pregnancy outcome in a prospective cohort Investigation of impact of aerobic exercise on course and outcome of pregnancy Prospective study of exercise

Author(s)	Type of study	Criteria definitions
Hume et al. (1990)	Prospective study of efficacy of exercise in pregnancy guidelines (U.S.) to predict pre-eclampsia	
Ramirez et al. (1990)	Investigation of occupational physical activity and risk of preterm birth	Pre-term delivery: ≤37 weeks gestation
James (1990)	Letter re physical exercise in U.S. military women (and pregnancy)	
Meeks (1986)	Review of the relationship between exercise and reproductive function	
Watson et al. (1991)	Study to assess fetal responses to maximal exercise, comparing cycling and swimming	25 and 35 weeks' gestation
Snyder (1990)	Review of aerobic exercise during pregnancy	

Author(s)	Type of study	Criteria definitions
Cumming and Rebar (1983)	Review of exercise and reproductive function	
Ruissen et al. (1990)	Investigation using measure- ment of umbilical blood flow and exercise	Moderate exercise: 20 deep knee bends
McMurray and Katz (1990)	Review of thermoregulation in pregnancy	
Brooks et al. (1984)	Letter re diet and athletic amenorrhoea	
Mansfield and Emans (1989)	Review of the impact of exercise and nutrition on menstrual cycle	2° amenorrhoea: ≤1 period pyear or absence of 3 periods
Bullen et al. (1984)	Investigation of hormonal effects of moderate exercise	
Huch and Erkkola (1990)	Review of risks and benefits of exercise during pregnancy	
Jarski and Trippett 1990)	Review of risks and benefits of exercise during pregnancy	
Fishbein and Phillips 1990)	Review of safety of exercise during pregnancy	Exercise: aerobic activity; herate increased to 70% maximizate for 12-15 min

nple size asures	Etiological links to infertility	Conclusions re fertility status
	Delayed menarche, shortened luteal phase, amenorrhoea; etiology was unclear but a variety of biopsychosocial factors were indicated	Exercise-associated defects in reproduction reversible by changes in lifestyle
atility index of umbilical ry	No differences in pulsatility indexes after moderate exercise irrespective of maternal or gestational age	
	Suggested link between exercise and hyperthermia in pregnancy	No data to suggest that normal pregnant women exercised to a level of exertion to cause hyperthermia
26	Regularly menstruating women (n = 15) ate 5x more meat than women with amenorrhoea (n = 11)	Vegetarian diet associated with amenorrhoea in athletes
	Hypothalamic disturbance	Prevalence of menstrual dysfunction in exercising women was higher than previously estimated
7 college women; um hormones, urine mones, aerobic capacity	n = 4: ovarian function disturbed, decreased estriol/free progesterone	Attempts to become pregnant may have been unsuccessful for women with disturbed ovarian steroids
	Theory: fear of pre-term labour as consequence to exercise; factors: hyper-thermia, infertility, high altitudes	Mild to moderate exercise was safe for women with normal pregnancies
	Potential risks: hypoxia, hyperthermia, heart changes	Literature provided no etiological risks to infertility or pregnancy
		Some evidence of risk of pre- term delivery, spontaneous abortion, and low-birthweight infants

Author(s)	Type of study	Criteria definitions
Cumming (1991)	Review of exercise and reproduction	
Sady et al. (1990)	Investigation of cardiovascular response to exercise during pregnancy	
Pivarnik et al. (1990)	Investigation of plasma volume and protein during exercise in pregnancy	
Carpenter et al. (1990)	Investigation of weight gain during pregnancy and exercise	
Durak et al. (1990)	Investigation of uterine response to exercise	Uterine contraction: tocometer deflection >15 mn Hg above baseline for <30 seconds
Katz et al. (1990b)	Investigation of effect of immersion and exercise on prolactin response	

nple size asures	Etiological links to infertility	Conclusions re fertility status
	Most runners' patterns of gonadotropins were suggestive of hypothalamic pituitary inhibition	Infertility reversible by decreasing amount of exercise
9 women; exercise tests, gen uptake, heart rate		Augmental cardiac response to exercise reduced 2 months post-partum
= 16 pregnant women; od sample: plasma otein		Some indication of risk for pregnancy-induced hypertension
= 10 pregnant women; ygen uptake, treadmill		Increased weight in pregnancy accounted for 75% of oxygen uptake in exercise and contributed to reduced exercise capacity
= 12 pregnant women; infold test, blood pressure, art rate, uterine activity	Use of bicycle ergometer led to uterine activity in 50% of sessions	Upper body ergometer and recumbent cycle were safest exercises
= 12 pregnant women; rum prolactin ergometer	Prolactin levels decreased significantly at each gestational age and post-partum during immersion	Physiological cause of prolactin decline lies in hypothalamic-pituitary system or peripheral circulation

Appendix 3. Summary of Literature Review: Nutrition

Author(s)	Type of study	Diagnostic criteria definiti
Van Der Spuy (1985)	Review of the impact of undernutrition and malnutrition on reproductive function	Fecundity: reproductive capacity; fertility: reproducti performance
Warren (1983)	Review of the effects of undernutrition on reproductive function	
Pirke et al. (1986)	Investigation of the effects of vegetarian vs. non-vegetarian weight loss diets on menstrual function	
Lunn et al. (1984)	Investigation of nutritional effects on lactation	
Landon et al. (1986)	Case study of pregnancy and nutrition	

nple size asures	Etiological links to infertility	Conclusions re fertility status
	Weight loss of 10%-15% body weight retarded pubertal development or caused 2° amenorrhoea post-menarche; hypothalamic origin of weight-related amenorrhoea, pituitary and ovarian function intact; low maternal weight was linked to low birthweight in infants, increased risk for perinatal mortality	Infertility reversible once normal body weight was restored; suboptimal nutrition did not always cause infertility
	Syndromes associated with undernutrition: AN, bulimia, weight loss, and post-pill amenorrhoea; exercise; hypothalamic disturbance indicated in AN	Infertility caused by undernutrition was reversible
= 18 healthy women; iight, blood: LH/ FSH, ogesterone, estradiol	7 women on a vegetarian diet: decreased LH (mid-cycle and luteal phase); decreased estrogen and progesterone (luteal phase); 7 women who were non-vegetarians maintained their ovulatory cycles	Vegetarian diet had adverse effects on fertility
= 240 lactating Gambian omen; hormone assays: olactin, estradiol, ogesterone	When diet improved, prolactin decreased; prolactin was central to initiation and maintenance of milk production, lactation, and birth spacing	Durations of lactation and infertility were closely related to plasma concentrations of prolactin
= 1 pregnant woman with N	Profound weight loss during pregnancy; supplementary feeding at 27 weeks; growth- retarded infant at term; at 6 months post-natal assessment, no developmental delay was observed	Undernutrition and weight loss were risks for low birthweight; no apparent long-term effects on a normally fed infant

Author(s)	Type of study	Diagnostic criteria definitio
Shatrugna et al. (1982)	Investigation of prolactin levels in undernourished Indian women	
Lunn et al. (1980)	Investigation of influence of maternal diet on plasma prolactin levels during lactation	
Huffman (1983)	Review of mother and child nutritional status and risks during pregnancy	Nutritional status: anthropometry, biochemical, clinical
Farthing et al. (1982)	Investigation of prevalence of infertility in men with celiac disease	Jejunal biopsy
Farthing and Dawson (1983)	Investigation of semen quality in men with Crohn's disease	

nple size	Etiological links to infertility	Conclusions re fertility status
57 lactating women; actin levels	Hyperprolactinaemia linked to infertility in lactating women	
30 U.K. women; 119 lactating Gambian nen; blood: prolactin	Hyperprolactinaemia caused infertility without involvement of other hormones; it also caused amenorrhoea	Improvement in nutritional status decreased lactational infertility
	Most studies indicated few etiological links between maternal nutritional status and capacity for pregnancy	Correlation between breast feeding and fertility was dependent on infant sucking patterns
28 men with celiac ease; n = 19 men with hn's disease; interviews, ninal analysis	Hypogonadism and abnormal semen in men with celiac disease	Pathogenesis of infertility unclear in celiac disease, but i may have been related to nutritional deficiency
13 men with Crohn's ease; n = 16 men with eac disease; semen alysis, weight	Oligospermia in 40% of the men with Crohn's; disordered sperm motility in both Crohn's and celiac diseases	Nutritional status was a factor in infertility in Crohn's and celiac diseases

Appendix 4. Summary of Literature Review: Obesity

Author(s)	Type of study	Criteria definitions
Friedman and Kim (1985)	Review of obesity and reproductive function	Massive obesity: >175% ide body weight
Whitaker (1987)	Review of obesity and reproduction	Obesity: >120% ideal body weight
Bates and Whitworth (1982)	Investigation of weight reduction on plasma androgens in obese infertile women	Obesity: ≥120% ideal body weight (Metropolitan Life tabl
Kim et al. (1982)	Investigation of cause of anovulation in obese women	Massive obesity: >175% idea body weight
Deital et al. (1988)	Investigation of gynaecologic/ obstetric changes after weight loss, post-bariatric surgery	Obesity: ≥ twice ideal body weight (Metropolitan Life table 1983)
Kopelman et al. (1980)	Investigation of hormonal status in massively obese women	Massively obese: 180%-1709 ideal body weight: medium frame, Metropolitan Life tables 1983
Kusakari et al. (1990)	Investigation of delayed reaction type luteinizing hormone releasing hormone (LH-RH) test and obesity in sterile women	Obesity: Japanese version of Broca's index
Printen and Scott (1982)	Retrospective chart review of the pregnancy following surgical treatment of obesity	Morbid obesity: twice ideal body weight for any given hei

Author(s)	Type of study	Criteria definitions
Bohrer and Kemmann (1987)	Investigation of risk factors for miscarriage in menotropin-treated women	
Hargreave et al. (1988)	Investigation of estrogen levels in men attending infertility clinic	
Stanik et al. (1981)	Investigation of effects of weight loss on reproductive hormones in obese men	Moderate obesity: 118%-208 of ideal body weight
Gross et al. (1980)	Investigation of pregnancy risk factors and neonatal outcome associated with maternal obesity	Obesity: >90 kg at some poil during pregnancy
Strain et al. (1982)	Investigation of pituitary-gonadal axis in obese men	

nple size sures	Etiological links	Conclusions re fertility status
154 infertile women who a treated with menotropin	Obesity and age >35 yrs.: risk factors for miscarriage	Women weighing >81 kg should lose weight prior to drug treatment for infertility
451 subfertile men; 80 fertile men; estradiol, y weight, fat	No differences in estradiol between both groups; no association between weight, body fat, and estradiol levels	Estradiol levels provide no prognostic information re future fertility
24 men; weight loss diet: calories per day	Normalization of hormonal values with weight loss	Abnormalities in moderately obese men were corrected with weight loss
2 746 consecutive veries; n = 279 obese nen	No differences between obese/non-obese at 1st and 2nd stages of labour	Obese mothers were at less risk for labour complications than was previously believed
21 obese men, n = 24 trols; plasma test: erane, LH, FSH; sperm lysis	Hypogonadotropic hypogonadism in obese men, but normal libido and potency	Abnormality due to partial suppression of pituitary

Appendix 5. Diagnostic Criteria for Anorexia Nervosa

- A. Refusal to maintain body weight over a minimal normal weight for age and height (e.g., weight loss leading to maintenance of body weight 15 percent below that expected; or failure to make expected weight gain during period of growth, leading to body weight 15 percent below that expected).
- B. Intense fear of gaining weight or becoming fat, even though underweight.
- C. Disturbance in the way in which one's body weight, size, or shape is experienced (e.g., the person claims to "feel fat" even when emaciated, believes that one area of the body is "too fat" even when obviously underweight).
- D. In females, absence of at least three consecutive menstrual cycles when otherwise expected to occur (primary [1°] or secondary [2°] amenorrhoea). A woman is considered to have amenorrhoea if her periods occur only following hormone (e.g., estrogen) administration.

From the *Diagnostic and Statistical Manual of Mental Disorders*. 3d ed. rev. Washington, DC: American Psychiatric Association, 1987.

Appendix 6. DSM-III-R Diagnostic Criteria for Bulimia Nervosa

- A. Recurrent episodes of binge eating (rapid consumption of a large amount of food in a discrete period of time).
- B. A feeling of lack of control over eating behaviour during the eating binges.
- C. The person regularly engages in self-induced vomiting, use of laxatives or diuretics, strict dieting or fasting, or vigorous exercise in order to prevent weight gain.
- D. A minimum average of two binge eating episodes a week for at least three months.
- E. Persistent overconcern with body shape and weight.

From the *Diagnostic and Statistical Manual of Mental Disorders*. 3d ed. rev. Washington, DC: American Psychiatric Association, 1987.

Glossary

Adrenocorticotropic hormone: Secreted by the anterior pituitary gland. Has a stimulating effect on the adrenal gland.

Amenorrhoea: Absence or loss of menstrual function.

Anovulation: Absence of the discharge of an ovum from the ovary during the menstrual cycle.

Celiac disease: A malabsorption syndrome affecting both children and adults, in which there is an inability to digest and utilize gluten-containing foods (fats, starches, and sugar).

Crohn's disease: Inflammation of unknown cause involving any part of gastrointestinal tract, most commonly involving the terminal ileum.

DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association, 3d ed., rev., 1987.

Ectopic pregnancy: Pregnancy in which the fertilized ovum becomes implanted outside the uterus instead of in the wall of the uterus.

Estradiol: An estrogenic hormone.

Follicle-stimulating hormone: Gonadotropin secreted by the anterior pituitary gland. Stimulates the growth and maturity of graafian follicles in the ovary.

Gonadotropin: Any hormone having a stimulating effect on the ovaries or testes. Follicle-stimulating hormone and luteinizing hormone are gonadotropins.

Growth hormone: Secreted by the pituitary gland. Controls general body growth, particularly the growth of the skeleton, and also influences metabolism.

Hyperthermia: Greatly increased temperature.

Hypothalamus: A portion of the brain. It is the coordinating centre for the autonomic nervous system. Also regulates body temperature and the secretory activity of the anterior lobe of the pituitary gland.

Hypoxia: Diminished availability of oxygen to the body tissues.

Luteinizing hormone: Gonadotropin secreted by the anterior pituitary gland. Acts with follicle-stimulating hormone to cause ovulation. It is also involved with corpus luteum formation.

Nullipara: A woman who has never given birth to a viable infant.

Oligomenorrhoea: Abnormally infrequent menstruation.

Pituitary: The master gland of the endocrine system. It controls hormone production of other endocrine glands. It is connected to the hypothalamus, which controls many of the functions of the pituitary gland by secreting hormonal substances, which in turn stimulate production of pituitary hormones.

Polycystic ovary syndrome: A condition characterized by oligomenorrhoea, amenorrhoea, anovulation, and infertility and is associated with polycystic ovaries.

Primipara: A woman who has had one pregnancy that resulted in a viable child. **Prolactin:** A hormone secreted by the anterior pituitary that promotes the growth of breast tissue and stimulates and sustains milk production.

Teratogenesis: The production of deformity in the developing embryo or fetus.

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Contraception: An Evaluation of Its Role in Relation to Infertility — Can It Protect?

B. Norman Barwin and W. Fisher



Executive Summary

This paper outlines current contraceptive methods and examines if they have any link to infertility or to adverse reproductive outcomes. Sixty-eight percent of Canadian women aged 18-49 are estimated to be practising contraception; thus, the topic is of great importance to the Commission. The need for guidelines to be developed regarding education about contraception, for increased access to services, for provision of counselling to people at risk regarding lifestyle modifications, and for the provision of leadership in sexual and reproductive health care promotion and prevention is documented.

This paper comprises the following sections:

 The Introduction addresses the prevalence of contraceptive use in Canada and describes the methodology used to conduct this study.

 "Contraceptive Methods" describes available contraceptive methods, their mechanisms of action, links to infertility, prevalence of use, and failure rates.

• "Contraceptive Use and Sexually Transmitted Diseases" (STDs) discusses how those individuals using contraceptives are also those more likely to be exposed to STDs and the impact of these on fertility.

 "Strategies for Prevention of Infertility Related to STDs by Appropriate Choice of Contraceptives" addresses prevention strategies, contraceptive research, and future policy directions, and the paper concludes with a series of recommendations.

Among this paper's recommendations to the Commission are the following:

- 1. That the government use its spending power and enforce standards of the Canada Health Act to ensure universal access to high-quality services that promote sexual and reproductive health for Canadians.
- That the government develop a long-term program financing strategy based on a disease prevention/health promotion model to replace its current curative approach to reproductive and sexual health.
- 3. That the government undertake research related to the diverse sexual and reproductive health needs of women, youth, cultural and linguistic minorities, physically and mentally challenged individuals, and others with distinct needs.
- 4. That the government improve the content, quality, and timing of delivery of programs to address the prevention of STDs and unplanned pregnancy.
- 5. That the government employ a comprehensive decision-making model rather than teach only abstinence and that it promote programs integrating protective decisions and behaviours at initial intercourse.
- 6. That professionals and the public be educated that the concomitant use of two contraceptive systems (dual protection) is necessary for both pregnancy control and the prevention of infection-based infertility. There is a need for public and professional education regarding the expert use of contraceptives with a view to protecting against unwanted pregnancy and an equal concern for future reproductive health.
- 7. That the media play a more positive role in the promotion of health protection conferred by highly effective contraceptives.
- 8. That both federal and provincial governments share the responsibility with industry in furthering research into newer, more effective, and safer contraceptives, as well as addressing the education, promotion, and delivery of services in pregnancy and STD prevention.

Introduction

Few issues have as great an impact on individuals, couples, families, and communities as those concerning reproductive health. Thus, it is important that safe, effective contraceptives be available to those wishing them. At the same time, Canadians must be assured that such contraceptives do not adversely affect their reproductive health and fertility.

Methodology

With these goals in mind, this paper reviews current contraceptive methods, assesses their effectiveness in preventing pregnancy, and documents whether they have any association with infertility or adverse pregnancy outcomes. Three hundred peer-reviewed research articles from the past 30 years were surveyed.

This literature review employed the most well-recognized computer data bases and other sources available, including MEDLINE, Index Medicus, Unique Identifier, InfoGlobe, Ontario Health Survey, Statistics Canada, and dissertation abstracts. Appropriate key words, including the names of all available contraceptives, all known sexually transmitted diseases (STDs), and terms such as "fertility," were used in the searches.

In addition, manual searches were undertaken on American College of Obstetrics and Gynecology data and the Alan Guttmacher Institute Resource File. Articles from scientific journals and other research sources in the fields of contraception and fertility and sterility research also were reviewed.

Canadian and non-Canadian sources have been reviewed; however,

this paper notes whenever Canadian data are unavailable.

The literature is inconclusive concerning the health effects of particular contraceptives. Thus, wherever possible, statistics in this paper represent the consensus of published topical reviews.

Contraceptive Methods

Introduction

Canada's first national fertility survey found that 68 percent of women aged 18-49 were practising contraception¹ (see Table 1). The mechanism of action, any association with unwanted infertility, prevalence of use (see Tables 2 and 3), and failure rates of each method are described below.

Contraception is widely practised so, ideally, family planning services must be user friendly, providing easy access to services, counselling, and the chosen contraceptive method. Professionals with responsibility for the advancement of contraception and the promotion of sexual health must consider birth control barriers as something broader than simply fertility control, and clients must be encouraged to safeguard their health over the long term — for example, by practising safe sex.

Table 1. Percentage of Distribution Prevalence of Female Contraceptive Users in Canada

Characteristic Number contraceptifves Occlusion Vasectomy Pill IUD Condom Other Never married 1 430 57.4 4.3 1.7 71.2 7.9 7.9 7.9 Age group 55.1 (0.4) (0.8) 84.1 4.2 5.9 4.6 25-34 35-49 101 49.5 32.0 2.0 24.0 18.0 18.0 Religion 752 57.2 2.3 74.5 81.4 4.2 5.9 4.6 Protestant 428 60.5 2.7 2.3 74.5 81.4 81.4 4.3 81.4 4.2 8.4 4.3 4.5 8.4 4.4 4.2 8.4 4.6 8.4 4.6 8.4 4.6 8.4 4.6 8.4 4.6 8.4 4.6 8.4 4.6 8.4 4.6 8.4 4.6 8.4 4.6 8.4 4.6 8.4 4.4 8.4 4.4 8.					% of those using contraceptives	oo buisr	ntracet	otives	
ed 1430 57.4 4.3 1.7 71.2 7.9 7.9 960 55.1 (0.4) (0.8) 84.1 4.2 5.9 7.9 369 65.9 7.4 3.7 51.4 14.0 12.8 1 101 49.5 5.2 7.4 3.7 51.4 14.0 12.8 1 428 65.2 57.2 5.3 1.6 68.9 7.9 7.9 7.9 550 51.6 3.9 (0.8) 74.5 8.1 8.1 8.1 8.1 516 68.8 59.7 6.3 17.4 10.6 2.2 7.1 14.1 3.7 517 66.3 76.1 6.1 6.5 6.5 0.4 6.5 6.5 0.4 525 67.1 58.0 4.7 27.0 14.1 3.7 6.9 6.9 6.9 6.9 6.9 6.9 6.9 6.9 6.9 6.9	Characteristic	Number	% using contraceptives	Tubal	Vasectomy		IND	Condom	Other
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960 55.1 (0.4) (0.8) 84.1 4.2 5.9 1369 65.9 7.4 3.7 51.4 14.0 12.8 1 101 49.5 32.0 2.0 24.0 18.0 6.0 1 12.8 1 101 49.5 32.0 2.0 24.0 18.0 6.0 1 12.8 12.8 12.8 12.8 12.8 12.8 12.8 12	Age group								
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752 57.2 5.3 1.6 68.9 7.9 7.9 7.9 7.9 7.9 7.1 256 60.5 2.7 2.3 74.5 8.1 8.1 8.1 257 6.3 74.5 8.1 8.1 8.1 37 59.5 9.0 2.0 59.4 27.3 4.5 24.5 75.1 43.6 7.4 27.0 14.1 3.7 252 67.1 58.0 4.7 21.9 10.1 1.8 252 67.1 58.0 4.7 21.9 10.1 1.8 253 64.0 7.5 14.3 8.7 0.6 254 65.1 53.6 7.1 14.3 15.5 6.0	35-49	101	49.5	32.0	2.0	24.0	18.0	0.9	18.0
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9 129 65.1 53.6 7.1 14.3 15.5 6.0	Protestant	219	73.5	64.0	7.5	14.3	8.7	9.0	2.0
	Other/none	129	65.1	53.6	7.1	14.3	15.5	0.9	3.6

Parentheses — fewer than 5.

Source: Modified from T.R. Balakrishnan, K. Krótki, and E. Lapierre-Adamcyk, "Contraceptive Use in Canada, 1984," Family Planning Perspectives 17 (1985): 209-15, and 1984 Canadian Fertility Survey.

Table 2. Advantages and Disadvantages of Contraceptive Methods

Method	Advantages	Disadvantages
Rhythm methods, natural family planning (NFP), periodic abstinence	Non-prescription User maintains personal control Requires communication between sexual partners Inexpensive No medical risk Always available	Inappropriate if menstrual cycle is irregular Requires motivation and intelligence No protection against STDs or HIV Unsuitable outside monogamous relationships High risk of failure
Coitus interruptus	Non-prescription/no cost Useful in emergency/ unprotected situations No medical risk Maintains user privacy Always available	High risk of failure Poor gratification Requires control by both partners No protection against STDs
Condom	Non-prescription Protects against STDs and HIV Inexpensive No medical risk Maintains user privacy Low risk of failure	Strong motivation required Occasional breakage/ slippage Some loss of sensation Occasional allergic reaction Pre-coital interference
Diaphragm	Safe, no systemic effects Used only when needed No effect on lactation No effect on future fertility Protects against STDs Reduced incidence of PID and cervical cancer (as barrier) Low risk of failure with spermicide	Requires motivation Requires intelligence and instruction in use Pre-coital interference ("messy") Requires privacy for insertion Risk of urinary tract infection
Vaginal cream, foam, suppositories	Non-prescription Minimal medical risk Privacy possible Protects against STDs Enhances effectiveness of vaginal barriers May protect against cervical neoplasia Low risk of failure if used with vaginal barriers	Requires strong motivation Requires correct application Occasional allergic reaction Pre-coital interference ("messy") High risk of failure if used without vaginal barriers

Method	Advantages	Disadvantages
Cervical cap	Reduces incidence of vaginitis Protects against STDs Less coital interference	Requires fitting by a physician Requires motivation Discomfort if poorly fitted Possible vaginal irritation High risk of failure
Sponge	Non-prescription Protects against STDs No medical risk	Requires strong motivation Possible burning sensation/ allergic reaction Difficult to remove Risk of infection if not removed after 24 hours High risk of failure
Vaginal condom	Protects against STDs No known medical risk Minimal pre-coital interference	Requires strong motivation Some loss of sensation
IUD	Maintains user's privacy Requires initial motivation only Low risk of failure	Risk of menorrhagia Risk of dysmenorrhoea Minimal increase in incidence of pelvic infection No protection against STDs
Combined oral contraceptives ("the pill")	Convenience Reversibility Privacy possible Potential health benefits Minimal risk of major side-effects No coital interference Reduces dysmenorrhoea, menorrhagia Regulates menstrual cycle Highly effective Reduces incidence of/ relieves premenstrual tension, acne, benign breast disease, iron deficiency/ anaemia, PID,	Requires prescription/ relatively high cost Requires instruction for use and daily motivation Affects metabolism and lactation Possible side-effects (breal through bleeding, amenorrhoea, drug interactions) Unsuitable for women olde than age 35, or those predisposed to cardio- vascular disease No protection against STDs

deficiency/ anaemia, PID, ovarian cysts, and ectopic

pregnancy

Table 2. (cont'd)

Method	Advantages	Disadvantages
Mini-pill (progesterone-only pill)	Convenience Reversibility Well tolerated No adverse effects on lactation No associated thrombotic, metabolic, or hypertensive problems Low risk of failure	Requires prescription/ medical supervision Requires daily motivation Disrupts menstrual cycle Risk of ectopic pregnancy No protection against STDs Less effective than com- bined oral contraceptives
Post-coital contraceptives ("morning-after" pill)	Useful in emergency/ unprotected situations Low risk of failure Side-effects (nausea, vomiting, bloating) Backup required for fai contraception/unprotectintercourse Possible teratogenic effects (nausea, vomiting, bloating) Backup required for fai contraception/unprotectintercourse Possible teratogenic effects (nausea, vomiting, bloating)	
Hormonal implants	Provides long-action protection May reduce anaemia Highly effective	Requires minor surgery for insertion and removal Possible irregular menstruation Small risk of ovarian cysts and ectopic pregnancy No protection against STDs
Injectable progesterones (Depo-Provera [®] , norethisterone oenanthate)	Convenience Privacy possible Prolonged protection Few metabolic effects Unrelated to timing of coitus Reversibility Useful when estrogen is intolerable Highly effective	Requires medical supervision Disrupts menstrual cycle Possible side-effects (spotting, weight gain, possible breast lesions, post-therapy amenorrhoea) Delayed return of fertility after discontinuation Contraceptive effect cannot be stopped at will

Table 2. (cont'd)

Method	Advantages	Disadvantages
Tubal ligation	Permanence Convenience Safety Requires initial motivation only Highly effective	Permanence Success of reversal not guaranteed Risk in operation/ anaesthesia Possible psychological repercussions Possible ectopic pregnancy in rare event of failure
Vasectomy	Minor procedure performed in physician's office/outpatient basis Permanence Low mortality if performed under local anaesthesia No coital interference No impact on health	Possible post-operative reaction (pain, infection, bleeding) Delay in onset of sterility (requires temporary additional contraceptive) Success of reversal not guaranteed

Source: B.N. Barwin, "Teenage Contraception," in *Adolescent Gynecology* and *Sexuality*, ed. B.N. Barwin and S. Belisle (New York: Masson Publishing, 1982), 92.

Table 3. Percentage of Pregnancies in First Year of Use

Contraceptive method	15-19	20-24	25-34	35-44
No method	90.0	95.0	87.5	75.0
Periodic abstinence	25.1-34.0	21.1-28.9	12.2-17.2	6.2-8.9
Condom	11.4-19.3	19.4-36.3	10.6-20.9	3.9-6.8
Diaphragm/cap	10.6-35.5	19.4-57.0	10.7-35.8	10.3-34.7
Sponge	14.1-47.3	25.9-76.0	14.3-47.7	13.7-46.3
Spermicides	29.7-35.0	33.0-38.7	24.3-28.8	9.1-11.0
IUD	2.2-6.3	2.6-3.8	3.3-3.8	1.7-3.9
Oral contraceptives	8.0-18.1	5.0-11.7	2.9-6.7	1.9-4.5

Source: S. Harlap, K. Kosk, and J.D. Forrest, *Preventing Pregnancy, Protecting Health* (New York: Alan Guttmacher Institute, 1991).

Given proper use, each contraceptive affords reasonable protection against pregnancy. Some barrier methods (e.g., condom or spermicide) also protect against traditional STDs, such as syphilis, gonorrhoea, chancroid, and lymphogranuloma venereum, and contemporary STDs, such as chlamydia, genital mycoplasma, bacillary vaginosis, human papillomavirus, herpes simplex virus II, and human immunodeficiency virus (HIV).

Choosing a Contraceptive Method

Choosing a contraceptive method is a complex process. Not only should the particular method, its chemical composition, and its method of use be considered, but its short- and long-term effects on future reproductive health and one's ability to bear children also must be considered.² Certain contraceptives may contribute to involuntary infertility, while others are considered to improve fertility.³ Thus, it is important to document the degree to which each method has a positive or negative impact on fertility over the long term, and whether a relationship exists between the duration of contraceptive use and the incidence of consequent infertility.

After using prescription or non-prescription contraceptives, it is disheartening for a couple and their physician to discover that the man or woman has an infertility problem. Having postponed childbearing to achieve financial, social, and educational goals, they may discover an unsuspected fertility problem after using oral contraceptives, intrauterine devices (IUDs), or a combination of methods. An increasing number of women delay childbirth until at least age 35 for economic reasons or to pursue educational or career goals. Such women tend to have a decreased ability to conceive (decreased fecundity rate). There are many reasons for this; for example, these women have had more time to acquire gynaecological disorders, such as endometriosis or pelvic inflammatory disease (PID), or become exposed to STDs that decrease one's fertility, as well as the normal background decrease in fertility with increasing age.⁴

It is difficult to predict whether users will develop a fertility problem after discontinuing contraceptive use. Many variables exist that must be taken into account in assessing any association between contraceptive use and infertility. These include the period of use, the user's sex and age, the number of sexual partners, and sexual behavioural patterns and lifestyle. Contraceptive users should carefully weigh the benefits of use of a particular contraceptive against its potential impact on general and reproductive health and fertility.

Persons suffering illness may be willing to assume the risks of taking drugs or undergoing an operation to improve their health; however, those simply wishing to prevent pregnancy do not want to assume such risks through contraceptive use. Unlike most other treatments or prescription drugs taken by people of childbearing age, contraceptives often are used for

many years. Thus, clients want modern birth control methods that are at least as safe in the short and long term as disease-treating methods.

The media have had a dramatic influence on the public's awareness and use of contraceptives. The media have been aggressive in reporting, often sensationally, problems associated with contraceptives. The results have often contributed to a public that is overly fearful of some of the most effective and safest contraceptives (e.g., oral contraceptives, IUDs, and Depo-Provera®). This portrayal has not been effectively countered with objective and balanced information.⁷

Contraceptives differ in their inherent ability to prevent conception; however, they differ even more in their ease of use and attractiveness to the

The health implications of a contraceptive include not only its direct effects but also the health effects of pregnancy and its outcome if the method fails. It is worth noting that the outcome of unintended pregnancy is almost as likely to be birth as induced abortion, whether the pregnancy resulted from contraceptive failure or lack of use.⁸

Table 1 illustrates the prevalence of contraceptive use among Canadian women by age, sex, marital status, and religious background.

Contraceptive Failure Rates

The choice of contraceptive is strongly affected by a woman's or couple's childbearing plans. For example, among women who intend to have children in future, the most popular contraceptives are oral contraceptives and the condom. Among women who have children and do not want any more, male or female sterilization is the preferred contraceptive. 9

Most women at risk of unintended pregnancy practise birth control. The pill is the most commonly used method (28 percent) and is reversible, followed by the condom (20 percent), also reversible. One-quarter of women at risk of unintended pregnancy rely on tubal ligation (25 percent); others rely on their partner's vasectomy (11 percent).

Women who intend to have a child in future are more likely to use a reversible contraceptive than those who do not plan a pregnancy.¹² Foam and barrier spermicidal methods are their most frequent choice.¹³

Contraceptive sterilization is the most frequently used method among mothers not intending to have more children. Six in 10 women at risk of unintended pregnancy who want no more children rely on contraceptive sterilization, namely, tubal ligation. The remaining mothers who do not want more children are as likely to use barrier or spermicidal contraceptives as they are to use the pill.¹⁴

Statistics indicate that about one in five women aged 15-19 at risk of unintended pregnancy uses no contraceptives. About one in 10 women in their 20s and one in 15 older women at risk of unintended pregnancy also use no contraceptives. ¹⁵

The pill is the contraceptive used most commonly in the early years of a woman's reproductive life. ¹⁶ Couples choose sterilization in increasing

numbers as pill use declines over the life cycle.¹⁷ The proportion of women at risk of unintended pregnancy who rely on sterilization rises from 21 percent of women aged 25-29 to 68 percent of women aged 40-44.¹⁸

The other contraceptive used by 20 percent of all women is the condom. Twenty-six percent of women aged 15-19 who are at risk of unintended pregnancy rely on the condom. Between 10 and 14 percent of older women also rely on the condom.¹⁹

Incorrect contraceptive use and subsequent method failure account for many unintended pregnancies and births; however, unprotected intercourse accounts for still more. Some contraceptives are associated with higher failure rates than others; for example, couples using a method that requires interruption of or abstinence from intercourse are more likely than others to experience contraceptive failure²⁰ (see Table 3).

Indeed, 47 percent of all unintended pregnancies occur while women are using a contraceptive method. About 41 percent of these pregnancies end in induced abortion and 46 percent result in births.²¹

Clearly, the user's ability and motivation to use a contraceptive carefully, correctly, and consistently has an important effect on its ability to prevent pregnancy.²²

1. Natural Family Planning

Natural family planning (NFP) means voluntarily avoiding coitus during the fertile phase of the menstrual cycle to avoid pregnancy. Couples in committed, monogamous relationships wishing to avoid steroid and intrauterine contraceptives may well choose NFP. The challenge for the professional in this situation is to be an expert teacher or to refer the users to experts such as Service, Regulation, Laissance Natility (SERENA) or the World Organization Ovulation Method Billings (WOOMB).

The effectiveness of NFP depends on accurately predicting when ovulation will occur or has occurred and abstaining from intercourse during that period. There are many ways to determine when the fertile period occurs, including the calendar rhythm or NFP methods known as the basal body temperature (BBT) method, the Billings mucus method, and the symptothermal method. Many researchers group these as "rhythm" methods, but others contend that rhythm describes only the least effective, calendar method.

The calendar method involves estimating the onset of ovulation and duration of a woman's fertile period on the basis of her menstrual history. The BBT method is based on the woman noting changes in her BBT. The mucus method involves noting the change in the consistency of the cervical mucus to determine ovulation. The symptothermal method combines the use of the cervical mucus and BBT methods with the additional noting of other signs of ovulation (e.g., ovulatory pain).²⁴

NFP is based on the following principles:

1. Ovulation occurs only once per month in each cycle.

- The interval between menses and ovulation may vary, but the 2. interval between ovulation and menses usually is constant at 12-16 days.
- Sperm may survive up to seven days, and the ovum may survive 3. 12-24 hours.
- High estrogen levels prior to ovulation increase the quantity of 4. cervical mucus. High levels of progesterone after ovulation result in a decrease in the cervical mucus, which also thickens in consistency. Progesterone also results in an elevation of BBT above the pre-ovulatory temperature.

Periodic abstinence may be favoured for religious reasons or to avoid a more "medical" contraceptive. Women with irregular periods or a history of cycles in which they do not ovulate are poor candidates for periodic abstinence techniques. Women with irregular temperature patterns also cannot use the BBT method.

Understanding and correct interpretation of NFP methods are the major factors in using these methods successfully. In addition to cooperation between partners, these methods also demand good communication, commitment, knowledge of one's reproductive cycle, maturity, and a monogamous relationship.25

In Canada. NFP is practised by less than 3 percent of married couples. These couples benefit from a fertility protection effectiveness of up to 90 percent. NFP is unpopular in less developed countries.

The 1984 Canadian Fertility Survey found that rhythm methods were used by 1.7 percent of never-married women and by 0.2 percent of previously married women.26

Despite its high failure rates, NFP prevents many pregnancies, since up to 88 percent of sexually active women would become pregnant within

a year without using any contraceptives.27

The high rate of unplanned pregnancies with NFP carries with it the attendant possibility of maternal morbidity (PID and infertility), abortion, and maternal mortality for non-monogamous women. NFP offers no protection against STDs and other genital infections, which, if they occur, increase the risk of PID.28

A risk of higher rates of birth defects has been suggested to be associated with fertilization of aged gametes;29 however, the rates of congenital malformation, stillbirths, and spontaneous abortions do not differ from those associated with other fertility-regulating methods or no method.30

A slightly higher male-to-female ratio among live births in women using this method has been found.³¹ Spontaneous abortion is more likely when insemination occurs four or more days after the temperature shift.³²

Couples practising periodic abstinence should be informed about potential problems, particularly when the woman is older (over 35) and has irregular periods, has a history of abortions, or has had children with birth defects.³³

Of all available methods, NFP leaves women most vulnerable to user failure because of the need to abstain during the fertile period and the need for sustained attention to physical changes and cooperation between partners. The symptothermal method is twice as effective as the cervical mucus method alone.³⁴ A combination of NFP and barrier methods or coitus interruptus may increase the efficacy of the measures above that of NFP and abstinence.³⁵

Effects on Health

No health complications are directly attributable to periodic abstinence; thus, the common assumption is that NFP is "healthier" for women than other contraceptives.

Periodic abstinence shares few of the risks of many other methods; however, it also shares few of the benefits. It results in more accidental pregnancies and, consequently, it also results in more spontaneous abortions and more Caesarian deliveries than would be expected among an equal number of women at risk for unintended pregnancy and practising another form of birth control.³⁶

2. Coitus Interruptus

This method involves the man withdrawing his penis from the vagina during coitus when he feels that ejaculation is imminent, to prevent pregnancy. It is widely practised, as it requires no medical intervention or supplies. It has no serious health risks.

Coitus interruptus is an ineffective method of birth control if the man has poor ejaculatory control or if he ejaculates before withdrawing his penis from the vagina. Even if he withdraws before ejaculation, pre-ejaculation fluid may have been left in the vagina and may contain sperm, which could result in pregnancy.

In Canada, about 4 percent of couples practise coitus interruptus; in Eastern Europe, however, this is the major method of contraception. Coitus interruptus is common among Catholics and among teenagers without access to services or financial resources.

Coitus interruptus does not provide any protection against the transmission of STDs, since infection may be present in uncontrolled ejaculate. Any resulting STD may have an impact on fertility if PID results. 37

3. Barrier and Spermicidal Methods

Condoms, diaphragms, and cervical caps used with contraceptive spermicide are reasonably effective at preventing pregnancy when used correctly and consistently.³⁸ The relatively high risk of failure associated with them is most often due to irregular and/or imperfect use.

Because couples must apply or insert these devices before intercourse,

they must interrupt intercourse or plan it ahead of time.

Women often complain that barrier and spermicidal methods are inconvenient or messy, and some men report decreased sensitivity with condom use.³⁹ Couples who find these devices inconvenient or unpleasant to use may be more likely to risk unprotected intercourse.

(a) Condom

A condom is a cylindrical sheath, usually made of latex rubber, that is rolled over the erect penis before intercourse to prevent sperm from reaching the female genital tract during intercourse. Mechanical barriers covering the penis have been in use for centuries to prevent pregnancy and infection.

Some men prefer condoms made from lamb's intestine, as they feel these condoms do not interfere with sexual pleasure; they also prevent allergic reactions to rubber or latex. Condoms may be sold lubricated or dry, straight or shaped, with or without a reservoir tip, transparent or coloured, smooth or textured. It should be noted, however, that only latex condoms are capable of protecting the user from the spread of STDs and HIV.⁴⁰ Condoms are non-prescription and are readily available over the counter and through vending machines.

Forty million couples worldwide use condoms as their sole or backup contraceptive. Condom use is low in Latin America, Africa, the Middle East, and most of Asia. In Canada and the United States, mean usage is 20 percent.

The 1984 Canadian Fertility Survey found that condom use tended to increase with user's level of education. There were no significant differences in the rates of use by Protestants and Catholics.⁴¹

Effective condom use demands correct, consistent use at every act of intercourse, strong motivation, and ready availability. Risk taking is probably higher among condom users than among users of other contraceptives. Used with spermicides, however, condoms are more than 99 percent effective as contraceptives. As Table 3 shows, older people using condoms have a lower pregnancy rate than younger couples who are more fecund, have sexual intercourse more often, and use condoms less consistently.

No risks to subsequent fertility and no health risks are attributable to condom use for either partner. Spermicides with the condom may cause minor reactions in either partner.

Barrier and spermicidal methods may differ in the health benefits that they provide. In theory, the condom should offer better protection than the diaphragm against STDs for men and women; however, studies show that diaphragm users have a lower incidence of STDs than women whose partners use condoms.⁴² The reasons for this are unknown.

(b) Diaphragm

The diaphragm is a soft dome-shaped rubber cup with a flexible rim that fits into the vagina and covers the cervix. A spermicidal gel or cream also is placed within the cup. The diaphragm may be inserted up to six hours before intercourse.

These prescription devices are available in several sizes and should be fitted by a physician or qualified health professional. Training in the proper placement and removal of the device is required. Some women cannot use the diaphragm because they are allergic to rubber or spermicide or because they cannot be fitted. Because of the possible risk of toxic shock syndrome, women should not wear the diaphragm for more than 24 hours.⁴³

The diaphragm provides a mechanical barrier to sperm entering the cervix, while the spermicide kills any sperm that may pass the barrier. The diaphragm should remain in place for at least six hours after intercourse. If additional intercourse occurs within that period, additional spermicidal gel, cream, or foam should be inserted into the vagina.

With the advent of modern contraceptives, diaphragm methods became less popular, as they were a more "messy" alternative and interferred more with sexual spontaneity. However, with concern over the health risks of oral contraception and IUDs, interest in the use of barrier methods has increased again. In Canada, about 4.9 percent of women use the diaphragm. ⁴⁴ In developing countries, 1-11 percent of contraceptive users choose the diaphragm.

As Table 3 indicates, the effectiveness is greatest among experienced older women.

The diaphragm appears to have no effect on future fertility. Its use significantly reduces the risk of PID. The prevention of PID and its possible attendant outcomes (ectopic pregnancy and involuntary infertility) is an important benefit of diaphragm use. Diaphragm users are less likely to have intercourse at an early age (under 20), and they have fewer sexual partners than users of oral contraceptives and IUDs. This means they are less likely to have subsequent infertility.

Toxic shock syndrome is rare among diaphragm users and has been reported in only one case, where the diaphragm was worn longer than 36 hours.⁴⁷ Spermicides may protect against toxic shock syndrome and reduce this risk.⁴⁸

The only known health risk associated with diaphragm use is that of urinary tract infection.⁴⁹ No other health risks are directly attributable to their use for either partner. Spermicides often used with the diaphragm may cause minor reactions in either partner.

Barrier and spermicidal methods are less effective than other contraceptives in preventing pregnancy; thus, users of this method will experience more Caesarian sections and complications of spontaneous abortions due to these unintended pregnancies. The diaphragm reduces the transmission of gonorrhoea and syphilis. Users of barrier and spermicidal methods will experience an estimated 53 percent fewer hospital

admissions for treatment of cervical cancer.⁵⁰ Perhaps the greatest benefit of barrier and spermicidal methods is that many hospital admissions for treatment of upper genital tract infections, ectopic pregnancies, and tubal infertility will be prevented.

Studies show that diaphragm users have a lower incidence of STDs than women whose partners use condoms. It is unknown whether women use the diaphragm more consistently than their partners use condoms, leading to a lower incidence of PID.⁵¹ (Limited data are available on the cap, on the sponge, and on spermicide used alone, but these methods are generally assumed to have effects similar to those of the condom and diaphragm.)

(c) Cervical Cap

Similar to the diaphragm, the cervical cap is smaller and depends on suction to stay in place, fitting close to the edge of the cervix. The cap is made of rubber, comes in several sizes, and must be fitted by a physician or other health professional.

The user places spermicide into the cap before placement into the vagina and must insert spermicide into the vagina if intercourse is to be repeated. The cervical cap may be inserted up to eight hours before intercourse and must be left in place for at least six hours after intercourse. It should not be left in place for any longer than 24-48 hours. It forms a mechanical barrier to sperm entering the cervix, and its spermicide also destroys sperm.

Fewer than 0.2 percent of women use this method. Use is more common among older women. Canadian statistics are unavailable; however, the rate of use probably is less than 0.2 percent.

There is no risk of infertility associated with the use of a cervical cap, and no side-effects on health have been reported. On rare occasions, cervical caps have been reported to cause lacerations, abrasions, or cervical suction marks after prolonged use. The use of the cap for more than three consecutive days probably promotes bacterial growth, but cervical or pelvic infection has not been reported among cap users. ⁵²

(d) Sponge

The sponge is a pliable polyurethane-foam disposable contraceptive measuring 5 centimetres in diameter and about 2.5 centimetres thick. This non-prescription device is impregnated with one gram of Nonoxynyl-9 spermicide, providing contraceptive protection for 24 hours, regardless of the frequency of intercourse. Sponges are moistened with water (to activate the spermicide) before being placed in the vagina and cover the cervix during intercourse.

The sponge releases spermicide, acts as a barrier, and absorbs sperm. The sponge can be inserted several hours before intercourse and must be left in place up to six hours following intercourse. It may be worn up to 24 hours.

The sponge's potential side-effects are similar to those of other spermicidal methods; namely, a burning sensation or an allergic reaction to the spermicide.

The sponge protects against the ascent of STDs into the genital tract, thereby reducing the potential for PID and possible subsequent infertility

from this.53

Sponges are mostly used by teenagers, as a backup to oral contraceptives, to prevent STDs. Surveys show use ranges from 1 to 15 percent in Canada. Canadian prevalence rates have not been evaluated, since the sponge has just recently been approved in Canada. ⁵⁴

As Table 3 indicates, failure rates among sponge users are high. There

is no direct infertility associated with sponge use.

The estimated risk of toxic shock syndrome for sponge users is similar to that for tampon users; that is, about five cases per 100 000 users. Thus, it is important to remove the vaginal sponge within 24 hours of insertion.

Data documenting non-contraceptive benefits of the sponge are limited; however, benefits associated with spermicide use probably also apply to sponge use. Sponge use has been found to significantly protect against chlamydia and gonorrhoea. The amount of spermicide in each sponge (one gram) is larger than the amount in one application of other products.

(e) Vaginal Condom

This new barrier contraceptive is designed for use by women. The vaginal condom is lubricated and is intended for one-time use. It does not

require professional fitting or precise placement over the cervix.

The vaginal condom consists of a soft loose-fitting polyurethane sheath and two flexible polyurethane rings. One of the rings lies inside the closed end of the sheath and serves as an insertion mechanism and internal anchor. The other ring forms the external edge of the sheath and remains outside the vagina after insertion, protecting the labia and the base of the penis during intercourse.

Clinical studies are being carried out to determine the prevalence of use and failure rate. Pre-clinical studies show that the polyurethane sheath is HIV-impermeable and appears impermeable to most STDs. It does not disrupt intercourse because women insert it before initiating the act. The vaginal condom may fill a need for women who want to use

contraceptives and prevent STDs.55

No untoward health effects have been noted. The reduction of STDs and knowledge that this device can be used without a partner's initiative have tremendous health and psychological benefits for some women.

4. Spermicides

Spermicides include gels, creams, suppositories, and foams that can dissolve in the vagina. The active ingredient of such preparations usually is Nonoxynol-9, which immobilizes and kills sperm. ⁵⁶ When used without another contraceptive device, spermicide should be inserted into the vagina

shortly before intercourse for maximum effectiveness; it lasts for several hours. Spermicide is most effective when used with a diaphragm, cap, or condom.

Some users complain of a slight burning sensation with use; others are allergic to spermicides and cannot use them or cannot use certain brands. Other active agents in spermicides also include octoxinol-9, benzalkonium chloride, and menfegol (not available in Canada).

Fewer than 5 percent of women use this method in developed countries, and even fewer use it in developing countries. In Canada, the prevalence of use is 0.4-2.8 percent.⁵⁷ The method's low rate of effectiveness affects the degree to which it is used. In addition, it is not readily recommended by physicians and often not carefully supervised.

As illustrated in Table 3, the failure rate of spermicides used as contraceptives is relatively high. Failure results from inconsistent or improper use, poor motivation, and the user's inability to follow instructions.

No evidence suggests impairment of fertility following contraceptive use of spermicides. They may be chosen because of the absence of side-effects, but they provide limited protection and are not recommended as a single method of contraception, ⁵⁸ although consistent correct application reduces the failure rate. The greatest value of spermicides is in augmenting the effectiveness of barrier contraceptives and IUDs and thus reducing the likelihood of STD transmission. ⁵⁹

Spermicides act to damage sperm; it is unlikely that a damaged sperm could cause fertilization. However, Jick and colleagues raised the question of whether there is an association between major congenital malformations and vaginal spermicides used within 60 days of conception. The question of whether there is an increased risk of spontaneous abortion was also raised. One study showed a small increase in congenital malformations among infants conceived as a result of contraceptive failure. This has not been confirmed by others, and there is no evidence that use of Nonoxynol-9 increases the risk of spontaneous abortion, multiple pregnancy, or birthweight or sex ratio abnormalities. There is no demonstrated association between major malformations and spermicide use, and no statistically significant evidence that spermicides cause major malformations if used before or at conception. In one study, fetal malformation was found to occur less often among women who use spermicides than among those who reported never using contraceptives.

One study showed that the proportion of female births was 25% higher in women who used spermicides around the time of conception than among the non-users. Those who used spermicides after conception were found to have approximately double the rate of fetal loss experienced by former users and this may have been associated with chromosomal abnormalities. 65

However, more recent studies have failed to show adverse fetal effects or poor reproductive outcome. 66 No well-defined pattern of defects has been

observed, as would be expected if these risks were related to spermicidal use. No warning label of possible teratogenic effects is required by the U.S. Food and Drug Administration (FDA) after review of the study data. ⁶⁷

5. Intrauterine Contraceptive Devices

The IUD was first described by Richter in 1909 and was made of silkworm gut and ring shaped. Today, the IUD is made of polyethylene that may have copper, silver, or medication added, and is made in various shapes and sizes. Once the device is inserted into the uterus, the user needs only to check to insure that the device is not expelled. A physician usually inserts the device into the uterus, where it remains in place for three to five years. Most modern IUDs contain copper; however, a progesterone IUD slowly releases a natural hormone (Progestasert) and must be replaced after one year of use.

The IUD achieves its contraceptive effects in several ways: preventing fertilization through disruptive effects on the sperm or sperm transport; or initiating a local inflammatory response to a foreign body (the IUD itself) within the uterine cavity, thus inhibiting implantation should fertilization occur.⁷⁰

Common problems associated with IUD use are break-through bleeding, pain, partial or complete expulsion of the device, and retraction of its string into the uterus. Potential side-effects of different IUDs are similar, except that the copper IUD tends to increase menstrual bleeding and the progesterone IUD appears to decrease it.⁷¹

Major risks associated with IUD use include PID, ectopic pregnancy, and perforation of the uterus. These may have a major impact on future reproductive health. The incidence of PID among IUD users may be related to the number of sexual partners and thus the greater risk of exposure to STDs 72

About 40 million women in the People's Republic of China and another 20 million women worldwide use IUDs. Of married women of reproductive age in Canada, about 1.8 percent use IUDs. ⁷³

According to various studies, pregnancy rates range from 0.5 percent to 5 percent per year. Pregnancy rates are lower for parous women than for non-parous women and are lower for all women over age 30. The risk of pregnancy decreases with time, and the devices bearing higher amounts of copper result in lower pregnancy rates. The ideal IUD candidate is a woman in a stable relationship or an older woman who has had a desired number of children. With the availability of information linking the Dalkon Shield® with a high incidence of PID and septic abortion, the incidence of IUD use decreased significantly since 1970.⁷⁴

Association of IUD Use with Subsequent Infertility

Concern about IUD use centres primarily on whether it affects the incidence of PID and, as a consequence, future fertility.⁷⁵ Even if certain assumptions are made, it is difficult to define PID to evaluate its degree of

severity. The development of pelvic adhesions as it relates to subsequent infertility depends on many variables, including the incidence, treatment patterns, progression, and recurrence of the disease process.

Studies have not demonstrated impaired fertility among women who discontinued IUD use to seek pregnancy. A cumulative pregnancy rate of 84.6 percent was reported within one year among 553 women who had

used the copper-T IUD.77

IUD use among 515 patients with salpingitis was compared with that of 941 (non-IUD users) sexually active control patients. The frequency of IUD use in patients with salpingitis was significantly higher (p > 0.001) in study patients than in the control group. The increased risk of PID for never-pregnant women was sevenfold. A significant increase was found in the frequency of diagnosis of PID among both inpatient and outpatient IUD users compared to users of oral contraceptives or diaphragms. No prolonged delay in the return of fertility was found in parous women who had the IUD removed to plan a pregnancy. PID of sufficient severity to impair fertility also would have been treated by removing the IUD.

The association between IUD use and PID was confirmed by laparoscopy. The risk of tubal blockage and the possibility of infertility increases from 10 percent after one PID episode to 75 percent after three episodes. Acute PID had an adverse effect on future fertility, and one of four women with PID subsequently experienced chronic abdominal pain, infertility, and/or ectopic pregnancy. The risk of infertility for up to five years ranged from 6.1 percent after a mild PID attack to 30 percent after severe PID attacks. In studies, past IUD use has been reported more commonly among patients with primary tubal infertility than among control groups. However, the relative risk is small, and is almost insignificant among users of copper-bearing IUDs. Sa

Tubal damage is the primary cause of infertility, and treatment is unlikely to be successful.⁸⁴ For this reason, nulliparous women should not use IUDs.⁸⁵ Ectopic pregnancy associated with septic abortion may impair fertility.⁸⁶ Perforations of the uterus that may require surgery may result in adhesions and impair fertility.⁸⁷

At the time of IUD insertion, micro-organisms in the cervix and vagina may enter the uterus.⁸⁸ In the first month after insertion, the likelihood of PID is about four times higher among IUD users than among women using no contraceptive; however, the risk falls quickly over time. IUD users experience fewer pregnancies,⁸⁹ and so have a lower incidence of upper genital tract infections associated with childbirth or abortion.

Among women in non-monogamous relationships, use of the IUD as a birth control measure can greatly influence the risk of upper genital tract infection and consequent risk of infertility. No method, periodic abstinence, and IUDs are poor contracentive chaines for such women.⁹⁰

and IUDs are poor contraceptive choices for such women.90

The mode of action of IUDs is poorly understood, and the reason for their failure to prevent pregnancy is unknown; however, many pregnancies are attributable to incorrect placement of the IUD. 91 A pregnancy rate of

0.5-5 percent was found in women after one year of use. The cumulative pregnancy rate decreases each year. Factors that influence pregnancy rates include previous unnoticed expulsion of the IUD, perforation (complete or partial) of the uterus, displacement of the device in the cervical canal, and incorrect initial placement of the IUD in the uterus. 93

Pregnancy Losses

The risk of spontaneous abortion is about fivefold higher for IUD users than for non-users. ⁹⁴ Abortion occurs in about half of the pregnancies if the device is not removed and in 20-30 percent if the device is removed. ⁹⁵ The woman should see her physician if pain or bleeding recurs. Half of the spontaneous abortions occur in the second trimester. ⁹⁶ New data confirm that if an IUD is easily removed early in pregnancy, the pregnancy is more likely to result in a live birth than in spontaneous abortion. ⁹⁷

The Dalkon Shield® IUD has been associated with fulminating septicaemia and second-trimester septic abortions. A small number of deaths have been recorded, and these have occurred within 72 hours of the onset of symptoms. BIUDs known as Lippes Loops® and Saf-T-Coils® also have been implicated. The threat of septic abortion is not present if the threads do not extrude through the cervix. If the device cannot be removed by gentle traction and pregnancy continues, the physician and the woman must be alerted to symptoms of abortion and sepsis. Pyrexia, malaise, or bleeding must be treated promptly with antibiotics and evacuation of the uterus, and removal of the IUD.

Effects on Pregnancy

The likelihood of premature membrane rupture and premature labour is increased. The incidence of premature births is four times greater if the copper-T IUD is left in place than if it is removed. If the device cannot be removed (threads drawn into the uterus), the woman should be made aware of the increased risk of prematurity. Uterine bleeding has been noted before and after 28 weeks, but without ill effects to the mother or the fetus.

During labour, the need for manual removal of the placenta is reported to increase sixfold. The reason may be that the IUD affects the attachment of the placenta to the uterine wall. There is no evidence that past IUD use leads to complications during a subsequent pregnancy in which it is not used.

Ectopic Pregnancy

There is conflicting evidence concerning the potential association between IUD use and ectopic pregnancy. Some studies report a higher incidence of ectopic pregnancy among IUD users compared to non-users. ¹⁰⁴ Other studies show that IUDs reduced uterine implantation by 99.5 percent and reduced tubal implantation by 95 percent, but they did not limit ovarian pregnancy. No evidence was found that IUDs cause ectopic pregnancy in general, or cause ovarian pregnancy in particular. It was

found that IUDs are most effective in preventing intrauterine

pregnancies. 105

In summary, the IUD probably does not cause ectopic pregnancies per se, but it does not protect the predisposed woman from ectopic pregnancy. 106 There is no indication of a causal relationship between the use of the inert or copper-bearing IUDs and ectopic pregnancy. 107

Women with a history of PID or ectopic pregnancy who used IUDs for more than two years had a 2.6 times greater risk of ectopic pregnancy than women who used IUDs for less than two years. That risk persisted for one year after the removal of the device due to the gradual development of non-bacterial inflammatory changes in the fallopian tubes. ¹⁰⁸

IUD users are at greatest risk of ectopic pregnancy immediately after the IUD is removed because the foreign body reaction remains sufficient to alter tubal function but not to prevent implantation. Thus, pregnancy should be avoided for three months after removal of an IUD; however, this is not done in practice. Even if long-term users face greater risks than short-term users, IUDs do not increase the users' risk of ectopic pregnancies when compared to women using no contraception at all. 109

The incidence of ectopic pregnancies increased threefold after an acute salpingitis attack. The risk increases with repeated attacks of acute salpingitis. Previous ectopic pregnancy increases the likelihood of a second; thus, women with a history of ectopic pregnancies should not use IUDs. 111

The ratio of ectopic pregnancies associated with the progesterone IUD is higher than that associated with other IUDs. For this reason, use of this device has been largely discontinued in some countries. The possibility of ectopic pregnancy should always be considered if a woman becomes pregnant while wearing an IUD. To minimize this risk, women who have had PID or ectopic or tubal surgery and nulliparous women should not use IUDs.

Women who discontinue using IUDs run no higher risk than other women of giving birth to malformed or low-birthweight infants or of having a stillbirth or miscarriage (see Table 4).

Conception with an IUD in Place

If the device is removed during the first trimester of pregnancy, the risk of second-trimester fetal loss does not increase. If it is not removed, however, the risk of second-trimester fetal loss increases up to tenfold. There is no overall association between the presence of an IUD at conception and third-trimester fetal loss; however, if the IUD is in place at the beginning of the second trimester, the risk of third-trimester fetal loss does appear to increase. The current practice of removing the IUD (if its threads are visible) once the pregnancy is recognized eliminates these risks.

There is no evidence to suggest that copper-bearing or inert IUDs have a teratogenic effect. 115 The device is always extra-amniotic when pregnancy

occurs. ¹¹⁶ The congenital abnormalities described in a review of 15 million women were only a fraction of the expected number; for example, the report of an infant born with a benign fibroma of the vocal cord was less than the incidence expected in the normal population. Two cases of multiple limb reduction occurred in offspring of women using the Grafenberg ring and the Dalkon Shield[®], but the incidence of limb reduction was not increased by the presence of an IUD at conception.

Table 4. Outcome of Singleton Unplanned Pregnancies in Parous Women According to Contraceptive Failure

	Percentage of total pregnancies			
Group and outcome	Oral	Diaphragm	IUD	
Normal live birth	81.9	78.3	33.0	
Malformed	4.5	1.8	0.9	
Stillbirth	0.0	1.8	0.9	
Miscarriage	13.6	18.1	55.7	
Ectopic gestation	0.0	0.0	0.0	
Subtotal	100 (22)*	100 (166)*	100 (115)*	
Termination	(8)*	(56)*	(50)*	
Total	(30)*	(222)*	(165)*	

^{*} Number of pregnancies in parentheses.

Source: Modified from M.P. Vessey et al., "Fertility After Stopping Different Methods of Contraception," *British Medical Journal* (4 February 1978): 265-67.

Effects on Women's Health

The benefits of the copper-bearing IUD derive from its effectiveness as a contraceptive. Users of the copper-bearing IUD experience many fewer pregnancies than users of other methods. Thus, they will have fewer Caesarian deliveries, fewer hospitalizations, and fewer spontaneous or induced abortions.

Use of the progesterone IUD results in more ectopic pregnancies. ¹¹⁸ This IUD may carry some benefits because the progesterone reduces bleeding and should lead to lower rates of infection. ¹¹⁹ There is no proof that the progesterone IUD is associated with a lower risk of PID than the copper-bearing IUD. ¹²⁰ Women in a mutually monogamous relationship and using IUDs have a lower risk of STDs. Other potential complications

of copper-bearing IUDs are infection, anaemia (from iron deficiency), and perforation of the uterus at the time of insertion. Annual reinsertion of the progesterone IUD introduces a potential risk of perforation and infection each year, compared to the copper-bearing IUDs, which can be left in place for up to five years.

In summary, IUDs offer no protection against STDs and their consequent risk of tubal infertility; in fact, IUDs may contribute to PID and thus possible tubal infertility in some women. As we explained, there is some association between IUD use and the adverse pregnancy outcomes of spontaneous and septic abortions and prematurity. Ectopic pregnancies do not appear to be caused by the IUD per se, except in the period immediately after removal; however, because they do not prevent tubal implantation in sexually active women who are predisposed to this, there is an association.

6. Oral Contraception

Combined Oral Contraceptives

Combined oral contraceptives (collectively called "the pill") contain synthetically produced estrogen and progesterone. The amount of hormone in each pill may be the same throughout the cycle (monophasic pills) or may vary throughout the cycle (triphasic pills). Oral contraceptives contain lower doses of hormones today than in the past. 122

Combined oral contraceptives suppress follicle-stimulating hormone (FSH) and luteinizing hormone (LH) so that no egg is available for fertilization. In the few cases in which the pill does not prevent ovulation, it averts pregnancy by changing the composition of the cervical mucus. The sperm has difficulty penetrating the mucus and is unable to reach the uterus and fallopian tubes, where fertilization takes place. Oral contraceptives also slow transport of the egg in the fallopian tube and change the uterine lining to inhibit implantation in case of fertilization. 123

Frequent side-effects of oral contraceptives are spotting and break-through bleeding, nausea, weight gain, breast discomfort and enlargement, headaches, and chloasma (blotchy brown spots). Side-effects other than spotting and break-through bleeding are less common with today's pills than they were with the older, higher-dose formulations. The lower the dose of estrogen in the pill, the more likely spotting and break-through bleeding will occur.

Risks associated with use of the pill are higher for older women, smokers, those with high blood pressure, diabetics, and women with a history of deep venous thrombosis. Such women should not use the pill. 125

The pill has many benefits. 126 It is the safest reversible contraceptive available to date. 127 As Table 1 indicates, the pill is chosen overwhelmingly by women under age 30. As Table 3 shows, the pill is the most effective reversible means of preventing unwanted pregnancy. Its contraceptive effectiveness is reflected in pregnancy rates that range from 0.7 percent to

7.0 percent per year. These pregnancies may be related to forgetfulness, side-effects, lack of pill supply, impaired absorption, drug interactions, failure to take the pill correctly, or biologically poor absorption. Oral contraceptives also may fail even when full dosage compliance is maintained.

Fertility After Pill Use

The fertility of nulliparous (never pregnant) and multiparous (more than one pregnancy) women is temporarily impaired after stopping use of oral contraceptives, compared with that of women who discontinue other contraceptives. This effect becomes negligible after 42 months among nulliparous women and after 30 months among multiparous women. 128

These data show that the impairment was independent of the duration of use of oral contraceptives; there was no advantage to users in stopping use of oral contraceptives "for a break." More recent findings show a significant additional delay in the return of fertility after oral contraceptive use by nulliparous women aged 30-34 who used the pill for at least two years, compared with the experience of a control group of former users of the cervical cap. No permanent fertility loss was demonstrated after 72 months in this older group. 129

The fertility of nulliparous women is unknown, and pill use may be blamed for subsequent infertility when it may have been present all along. There is no evidence to indicate that use of oral contraceptives results in

permanent sterility. 130

There is also no evidence to substantiate a rebound effect or increased fertility after discontinuing oral contraceptives, and the pill should not be used for such a purpose. The initial delay in the return to fertility is partly explained by the mild prolongation of the first post-pill cycle (medium length about 35 days) and the initial tendency to anovulatory cycles. Conception rates are lower than normal only during the first three months after discontinuing oral contraceptives. "Normal" monthly fertility rates are restored, leading to "normal" cumulative rates after two years. 131

If secondary amenorrhoea (lack of menstrual flow) occurs without primary ovarian failure, normal rates of conception and childbirth can be obtained with available methods of investigation and treatment. Infertility following use of oral contraceptives is transient and reversible. Post-pill amenorrhoea poses no threat to fertility, regardless of the user's menstrual

history. 132

Secondary Amenorrhoea (Absence of Menstruation)

The return of spontaneous menses in women who discontinue oral contraceptives usually is prompt, occurring within 6-10 weeks in most cases. About 70 percent of women ovulate during the first spontaneous cycle, and 98 percent do so by the third cycle. Women should not expect cycles within the first three months after discontinuing oral contraceptives.

The cause of post-pill amenorrhoea has not been established; however, several observations have been made. Post-pill amenorrhoea does

not appear related to any particular compound. It is not related to the length of time the pill was taken, having been reported in women who took oral contraceptives for as few as three months. It also does not appear to be dose-related, since it has been reported in women who took various doses of both combined and sequential oral contraceptives.

Amenorrhoea occurred in 0.7-0.8 percent of women who had discontinued oral contraceptives for at least six months. ¹³⁶ In a study of the epidemiology of secondary amenorrhoea among Swedish women, the incidence of amenorrhoea was reported as 13.8 percent. Most of these cases were related to pregnancy. As expected, the rate decreases over a year. No relation could be found between the age at menarche (onset of first menstruation) or pregnancy history and incidence of secondary amenorrhoea. ¹³⁷ The low incidence of secondary amenorrhoea suggests no statistical correlation between the use of oral contraceptives and the occurrence of subsequent amenorrhoea. ¹³⁸ In some studies, up to half the women involved experienced amenorrhoea, menstrual irregularities, or late onset of menses before taking oral contraceptives; however, women without previous menstrual abnormalities also developed this condition. ¹³⁹

Some women also may develop galactorrhoea (inappropriate lactation) and have high levels of serum prolactin. Women with amenorrhoea, galactorrhoea, and high serum prolactin levels usually have normal to low levels of serum gonadotropins and estrogens. These patients usually respond to treatment with the resumption of menses, ovulation, and, in some cases, pregnancy. 141

Increasing numbers of couples are delaying childbearing into their late 20s and early 30s because of financial and/or educational considerations. It is especially important to advise individuals with abnormal menstrual patterns of the possibility of infertility following contraceptive use. The use of oral contraceptives produces artificially regular menses and may mask an underlying infertility. The provider of health care has an important role to play in counselling the user on the contraceptive's risk/benefit effects on future fertility and reproductive outcome.

Oral Contraceptives and Pregnancy Outcome

There are conflicting reports on the teratogenic hazard associated with use of oral contraceptives before or during the first month of pregnancy. Most reports, however, indicate that if there is any risk, it is negligible. Oral contraceptives taken before conception have shown no detectable adverse effects on the offspring. Anthropometric, psychometric, and haematologic measurements over the first three years of life showed no significant differences among children whose mothers used or did not use oral contraceptives before conception.

A relationship between drug ingestion and subsequent increased incidence of fetal abnormalities and other pathological states has not been demonstrated. 146

Some fetal malformations have been reported among the offspring of oral contraceptive users, including an increased incidence of fetal chromosomal abnormalities in spontaneously aborted fetuses among women who recently discontinued oral contraceptives. Genital masculinization among daughters of women who inadvertently took oral contraceptives during early pregnancy has been reported. A possible relationship has been documented between exposure to combined oral contraceptives and progesterone derivatives during pregnancy and subsequent birth defects. Vacterl (vertebral, anal, cardiac, tracheoesophageal, cardiac, cardiac, and limb reduction and the possible appearance of Down syndrome have been reported. However, many other studies have not been able to document any association.

Concerns have been raised concerning a possible causal relationship in a small number of women between previous use of oral contraceptives and defects including triploidy (three sets of chromosomes), other chromosomal abnormalities, and growth disorganization. However, the incidence of chromosomal abnormalities among 2 583 children of pill users did not differ significantly from that among 7 405 children of a control group of women. The Royal College of General Practitioners compared the outcome of 5 500 pregnancies among previous pill users with that of 11 000 pregnancies among a control group. There were 86 congenital abnormalities (a rate of 19.2 per 100 000) among offspring of former pill users versus 177 abnormalities (19.4 per 100 000) among the offspring of the control group. The ratio of these rates is 1.03 and is insignificant. Analysis of the abnormalities revealed no significant grouping in the vacterl group. The

Extensive chromosomal studies also were conducted in the context of 3 080 spontaneous abortions among three groups of women: those who had used oral contraceptives, those who had used non-hormonal contraceptives, and those who had not used contraceptives. The studies concluded that there was an abnormality rate of 6.8 per thousand for conceptions among women who had used oral contraceptives, and 4.9 per thousand among women who had never used contraceptives. This was not a significant difference, and the incidence of abnormalities decreased as the period of oral contraceptive use increased. The observed abnormality rate in this study agreed with the rate of 5.6 per thousand

obtained in another study of more than 43 000 babies. 161

Data were examined to see if there was any association between occurrence of Down syndrome and oral contraceptive use. One hundred and three mothers of Down syndrome infants and an equal number of mothers whose infants did not have Down syndrome were studied. The incidence of pill users was higher in the control group than in the group whose infants had Down syndrome, but the difference was not considered significant. There are no data to conclude that previous pill use is associated with an increased incidence of vacterl defects, Down syndrome, or triploidy in infants. This does not, however, settle the question of

incidence of defects in women who inadvertently take oral contraceptives during pregnancy. No significant association between neural tube defects and oral contraceptive use during pregnancy or before conception has been found. 164

Masculinization of the female infant is associated with oral administration of progesterone to mothers during the first trimester of pregnancy to prevent abortion; this is not the usual contraceptive pill. Clinical findings include phallic enlargement and, in some cases, varying degrees of labioscrotal fusion. The amount of progesterone and estrogen in oral contraceptives has been dramatically reduced since introduction of these birth control products. The literature does not report clinical evidence of masculinization of female infants born to women taking combined oral contraceptives containing one milligram of progesterone during early pregnancy. Although they do not cause detectable fetal abnormality, it is possible that ingestion of these compounds might produce minor, subtle abnormalities. Thus, women should stop using oral contraceptives whenever pregnancy is suspected. If desired, an alternative method of contraception should be commenced.

Diethylstilbestrol (DES) was also used to treat women at risk for abortion. DES should not be taken during pregnancy, as its use is associated with clear cell carcinoma of the vagina and cervix. 166

Recently, a disproportionate number of daughters was reported in a study of mothers who used oral contraceptives and delivered low-birthweight babies. ¹⁶⁷ However, upon re-examination of the initial data, it was concluded that the use of oral contraceptives, the duration of use, the interval between discontinuation of use of oral contraceptives, and subsequent conception have no bearing on the sex of babies born to oral contraceptive users. ¹⁶⁸

Hormonal contraceptives have been used to determine if a woman is pregnant, as absence of bleeding following withdrawal of the hormone signifies pregnancy.¹⁶⁹ Simpler, non-invasive tests exist; thus, use of hormones in this instance is unjustified.¹⁷⁰

In summary, the risk of major abnormalities in offspring because a woman is taking oral contraceptives is either minuscule or non-existent; however, oral contraceptives should not be used during pregnancy and should be discontinued if pregnancy is confirmed. There is no clear evidence of teratogenic effects of oral contraceptives before or during pregnancy.

It is theoretically possible that, rarely, abnormalities may result because some offspring may be genetically predisposed to anomalies. In such cases, the contraceptive hormones or their metabolic products may act with the abnormal genes to trigger the development of a specific malfunction. It may also be that low metabolic clearance of the hormones may lead to an abnormal accumulation of hormones and/or their metabolic products.¹⁷¹ These substances could be toxic to the embryo, either directly or by reducing the availability of vitamins crucial to fetal growth, such as

folic acid and vitamin B_{12} . ¹⁷² However, demonstrating any small associated increase in the incidence of rare abnormalities is formidable. The evidence in total shows no appreciable increase in congenital abnormalities.

Effects on Women's Health

Many pill users avoid hospitalization each year because of the pill's relatively low failure rate. There are also other effects. For instance, oral contraceptive use decreases the incidence of benign breast disease (the longer the use, the lower the incidence). Pill use also prevents hospital admissions for surgical removal of ovarian cysts. The pill's beneficial effects on the incidence of ovarian and endometrial cancer are nearly counter-balanced by the additional cases of breast and liver neoplasms that may occur among users. 175

Women using the pill are less likely to experience iron deficiency, anaemia, and severe menstrual pain. On the other hand, oral contraceptive users have more hospital admissions for gall-bladder disease than other women at risk for unintended pregnancy. Compared to other women at risk for unintended pregnancy, oral contraceptive users, especially older smokers, experience more hospital admissions for cardiovascular disease (myocardial infarction, stroke, episodes of venous thrombosis, and embolism). Transient side-effects of the pill include nausea, breast enlargement, weight gain or loss, dizziness, and pigmentation.

The Mini-Pill (Progesterone-Only Pill)

This alternative oral contraceptive contains only progesterone. It is often called the mini-pill because it contains considerably lower doses of hormones than combined pills. It does not suppress ovulation as effectively as the combined pill; thus, it is less effective in preventing pregnancy. The mini-pill prevents pregnancy by causing a thickening of the cervical mucus, slowing sperm transport, and inhibiting implantation by changing the uterine lining. Irregular bleeding, decreased duration of menstrual flow, amenorrhoea, and break-through bleeding are associated with use of the mini-pill. Fewer than 0.1 percent of Canadian women use the mini-pill. In the United Kingdom, the comparable figure is 7 percent. Ideal users are women for whom estrogen is contraindicated and older women.

The mini-pill is less effective than combined oral contraceptives. Its annual failure rate may be up to 2.1 percent. The effectiveness of use ranges up to 4.3 percent annually. Contraceptive failure among progesterone-only pill users is mainly due to incorrect use of the pill. The pregnancy rate diminishes with the age of mini-pill users because of the lower fecundity rate among older women of reproductive age.

There is no evidence of impaired fertility following use of the minipill. Women studied became pregnant within six months of discontinuing the mini-pill. There is no conclusive evidence of prolonged amenorrhoea after discontinuing the mini-pill. When used by breast-

feeding women, progesterone pills do not reduce the quantity and quality

Fewer than 1 percent of all oral contraceptive users take progesteroneonly mini-pills. The benefits and risks of these progesterone pills are not yet fully known. It is expected, however, that progesterone pills offer benefits similar to those of combined oral contraceptives. progesterone-only pill is expected to have a beneficial effect on PID and reduce the risk of ovarian cysts; however, there is some evidence of increased blood pressure associated with progesterone use. 183

Like the combined pill, progesterone-only pills do not protect against cervical cancer. Whether women using these pills will be at greater or lesser risk of disease than women using non-hormonal, non-spermicidal contraceptives with the same number of sexual partners is unknown.

High doses of progesterone taken early in pregnancy have been associated with congenital defects; 184 however, no congenital abnormalities have been reported among babies born to women taking the mini-pill at conception. Women should avoid taking the progesterone-only pill during pregnancy.

Post-Coital Contraceptives 7.

Combined oral contraceptives sometimes are used as "morning-after" pills following unprotected intercourse. To be effective, they must be taken within 72 hours after unprotected intercourse. The pill prevents implantation of the egg if fertilization has occurred. 185 Post-coital use of the birth control pill must be prescribed by a physician or professional. "morning after" pill contains D-norgestrel and ethynyl estradiol (Ovral). Two tablets are taken 12 hours apart. 186 This clinical application is not specified in the official approval of oral contraception by the Health Protection Branch of the Department of National Health and Welfare. The issue of possible teratogenicity in the wake of failed "morning after" pills has not been settled and has resulted in local policies where follow-up is sought in advance, since a therapeutic abortion is an option.

Another post-coital contraceptive is RU-486 (Mefepristone), a progesterone antagonist that prevents or terminates pregnancy by blocking

target cells in the uterus, thereby preventing implantation.

When tablets of RU-486 are taken orally for one to three days, progestational support for the endometrium (lining of the uterus) is interrupted and menstrual bleeding ensues. If this occurs in a month when fertilization has occurred, the fertilized egg or early embryo is discharged with the menstrual flow.

The effectiveness of RU-486 depends more on the length of time past fertilization than the dose used. When treatment is within 10 days after a missed period, the drug terminates pregnancy in 85 percent of cases. Using RU-486 with prostaglandin analogues increases the effectiveness of both drugs as abortifacients. When these drugs are used in combination, lower doses may be used with fewer potential side-effects.

In developing countries, most deaths among women of childbearing age are from complications of unclean abortion and pregnancy. In future, RU-486 may have a dramatic effect on the reduction of morbidity (including infertility) and mortality from these complications. RU-486 is not approved in Canada or the United States. However, new menses-inducing therapy is an important alternative to surgical termination of early pregnancy, although it is not a method of abortion suitable to be sold simply over the counter for use without clinical backup.

The prevalence of use of the post-coital pill is unknown, since it is used on an emergency basis. Failure rates range from 1 percent to 4 percent. The sooner treatment is commenced after unprotected coitus, the greater its effectiveness. Since post-coital contraception is used mainly after unprotected coitus (including rape and sexual assault), the risk of STDs is increased in these situations, and they may result in reduced fertility if not diagnosed or treated.

Apart from the side-effects noted in Table 2 (nausea, vomiting, bloating), there are no long-term health risks in use of post-coital contraceptives.

8. Long-Acting Hormonal Contraceptives

(a) Implants

Contraceptive implants are small capsules containing the progesterone Levonorgestrel that are implanted under the skin of a woman's upper arm. Norplant has been used in many countries for nearly 10 years. These implants slowly release a small amount of progestin and remain effective in preventing pregnancies for up to five years. Like other progestin-based methods, the implants inhibit ovulation, promote thickening of the cervical mucus, decelerate egg transport, and inhibit implantation of a fertilized egg. Once the implants are removed, menstruation ensues.

The common side-effects of implants are the same as those associated with progestin and mini-pills: irregular bleeding and spotting, decreased duration of menses, reduced menstrual flow, and amenorrhoea. The capsules are removed after five years, at the user's request, if there are any side-effects, or if unplanned pregnancy occurs.

Implants are unavailable in Canada; however, they have recently been approved by the U.S. FDA. They are widely used in developing countries, especially in South America. First-year failure rates range from 0.2 percent to 1.0 percent and increase slightly after five years (to 2.5 percent). There is no evidence of permanent infertility following use of implants; however, unpredictable delays in the return of fertility are common. This delay is similar to that experienced by former users of oral contraceptives or IUDs. No ill effects have been shown among women who use implants before or during pregnancy, on breast-feeding mothers, or on the quantity of milk produced. The use of implants is associated with reductions in iron

deficiency, anaemia, PID, dysmenorrhoea, premenstrual syndrome (PMS), and menopausal symptoms.

(b) Injectable Contraceptives (Injectable Progesterones)

Injectable contraceptives have been widely available for many years outside Canada. They contain progestin or a combination of progestin and estrogen. The most common formulations are medroxyprogesterone acetate (depot medroxyprogesterone acetate, Depo-Provera[®], or DMPA) and norethindrone enanthate (norethisterone oenanthate or NET). 190 Depo-Provera[®] is registered as a contraceptive in 90 countries worldwide and is used by more than 20 million women. Pregnancy rates for users of injectable contraceptives are lower than those for users of oral contraceptives (less than 1 percent per 100 women-years). 191

The action and potential side-effects of progestin-only injectable contraceptives are similar to those of the mini-pill and implants. Many long-term users develop amenorrhoea. Depo-Provera® has been approved by Canada's Health Protection Branch for treatment of certain gynaecological conditions (e.g., endometriosis) and menopause, but not as a contraceptive. Each injection maintains its contraceptive effectiveness for about three months, at which time the user must receive another injection. Side-effects include spotting, irregular bleeding, amenorrhoea, and weight gain.

Controversy has arisen around use of Depo-Provera[®] as a result of animal studies demonstrating possible links with cancers. Female beagles developed mammary tumours¹⁹³ and rhesus monkeys developed endometrial carcinoma after receiving Depo-Provera[®] at 50 times human doses. It has also been questioned whether an association exists between the drug and cervical cancer.¹⁹⁴ However, in human studies involving 5 000 women using Depo-Provera[®] for more than 40 000 women-years, the World Health Organization (WHO) found no evidence of a link between Depo-Provera[®] and an increased risk of developing breast, endometrial, or ovarian cancer.¹⁹⁵

No difference was found in the cervical cytology of women using IUDs and those using Depo-Provera[®]. ¹⁹⁶ A further WHO study showed a doubling of cervical cancer rates among women using Depo-Provera[®] for five years or more. Obviously, those using contraceptives are sexually active, which increases the risk of cervical cancer. It should be noted that this study included no controls and many personal variables; thus, its data cannot be considered conclusive. ¹⁹⁷

Delay in the return of fertility following contraceptive use reflects the drug's prolonged action. This depends on the release from the last injection site and may reflect individual differences in the rate of drug absorption and excretion. Ovulation returns once the blood levels of Depo-Provera fall below the critical level (0.1 mg) and is unrelated to the number of injections given. There is no evidence that the hypothalamic-pituitary axis is unable to recover after the drug has been eliminated. 199

Use of Depo-Provera[®] has been shown to cause a delayed return of fertility in the early months after discontinuation; however, by nine months, the proportion of women who did not conceive is similar to that of former IUD users. By three years, the proportion is similar to that of former oral contraceptive users. Return of menstruation is somewhat delayed (2-13 months) compared to former pill users.²⁰⁰

No long-term inhibition of ovulation or fertility was noted among women who received multiple NET injections. Conception rates were not markedly different from those among women who discontinued non-hormonal contraceptives or those who had used no contraceptives. After discontinuing Depo-Provera® or NET injections, users can expect a median delay of nine months or five months, respectively, before conception.²⁰¹

There is no evidence that injectable contraceptives cause persistent amenorrhoea or sterility. Prolonged amenorrhoea has not been reported after drug levels have fallen to zero. If desired, ovulation can be induced with human gonadotropins in women who have used injectable contraceptives. Experience with Depo-Provera has shown that the return of fertility is quickest among younger and thinner women. The return of fertility in nulliparous women resembles that of multiparous women.

Women should change to a mechanical contraceptive for at least six months before they plan to conceive and continue until two spontaneous periods have occurred. This will facilitate estimation of the expected delivery date. Women who are late for the date of the next injection by more than four weeks should be examined to exclude pregnancy before the next injection. They also should use extra precautions for the first two weeks after the injection. Former users of Depo-Provera[®] who conceived in the first month after discontinuation had similar pregnancy outcomes to those of women who conceived later. Those who did not conceive experienced bleeding problems similar to those of former oral contraceptive users.²⁰⁵

The frequent occurrence of amenorrhoea has raised the question of the reversal of Depo-Provera[®]. Generally, it has been concluded that the injectable drug delays but does not impair future fertility.²⁰⁶ Careful epidemiological investigations showed no association between the duration of Depo-Provera[®] use and the return of fertility. The effectiveness of injectable contraceptives means that ovulation and pregnancy are unlikely to occur until the Depo-Provera[®] has reached an undetectable level in the body.

Among former users who bore children, there was no increase in congenital abnormalities, stillbirths, or multiple births and no difference in the sex distribution of their babies.²⁰⁷

When Depo-Provera[®] was used in massive doses to prevent spontaneous abortion, a few cases of masculization of female infants were reported, ²⁰⁸ and treatment is therefore no longer recommended. However, Depo-Provera[®] does not appear to increase the risk of spontaneous

abortion, stillbirths, prematurity, or congenital malformations. No significant difference in birthweights was found among newborns whose mothers received Depo-Provera® before conception, those exposed *in utero*, and a control group.²⁰⁹ The intellectual and personality development of children born to women who used injectable contraceptives was found to be normal. These children were no different from a control group with regard to weight gain, incidence of childhood infections, bone growth, and incidence of abnormalities.²¹⁰

When the contraceptive injection is given during menstruation, the potential problem of infant exposure *in utero* is minimal. If injection is impossible at that time, the possibility of pregnancy should be excluded before administering the injection. There is no evidence of harmful fetal effects following the use of injectable contraceptives at doses that would permit conception.²¹¹

Because of the risk of heavy or prolonged bleeding among some women, injectable contraceptives should be used with caution post-partum, and delaying the first injection until five or six weeks post-partum makes this less likely. Most studies show no increase in the concentration of lipids, proteins, or lactose, or in the volume of lactation. Depo-Provera produces a slight accentuation of prolactin in response in breast-feeding mothers. Most studies report that Depo-Provera used during lactation has no effect on infant growth. Some studies have shown a beneficial effect. No differences in patterns of weight gain and incidence of infectious diseases were found between infants fed milk containing Depo-Provera and those who were not. Depo-Provera is believed to have no effect on the immunological benefits of breast milk.

9. Surgical Contraceptive Methods

(a) Tubal Sterilization in Females

Tubal sterilization (also called tubal ligation or tying of the fallopian tubes) involves surgery in which sections of each fallopian tube in women are blocked or severed so that the egg and sperm cannot meet.²¹⁶ Gamete (egg) transplant is interrupted by mechanical obstruction or by removal of segments of the fallopian tubes, which transport sperm and eggs.

Tubal sterilization can be performed either post-partum or at a time unassociated with delivery or abortion (interval sterilization). The procedure can be performed under local anaesthesia and on an outpatient basis. Sutures, electrocoagulation clips, bands, or rings are used to close or sever the tubes.²¹⁷

Tubal sterilization must be viewed as permanent and requires proper counselling. However, the procedure sometimes can be reversed with microsurgery (depending on the technique used, the length of tube destroyed during the initial operation, and the location of the tubal destruction). Such surgery can be complicated, extensive, and difficult, and success cannot be guaranteed.²¹⁸ The type of tubal occlusion is one of

the main criteria for dictating the potential success of reversal, which should be carried out by a reconstructive surgeon. The procedure is time-consuming, but the success rate is high (60-70 percent). Of such women who become pregnant, 15-20 percent experience ectopic pregnancies and 15 percent are at risk for spontaneous abortion.

Voluntary sterilization is the most popular method of contraception both in Canada and worldwide. It is relied on by almost 60 percent of all married contraceptive users and 66 percent of previously married contraceptive users. ²¹⁹ It is the only contraceptive method that keeps the risk of pregnancy at less than 1 percent without any user intervention.

The primary cause of failure of this contraceptive method is unrecognized conception that preceded surgery, which accounts for half of such pregnancies. Other failures may be attributed to operative error, spontaneous re-anastomosis (opening), defects in the clip, and early ectopic pregnancy. Each sterilization procedure carries a small chance of failure. In the rare event that a woman becomes pregnant after tubal sterilization, the probability of ectopic pregnancy is high. ²²⁰

The main health benefits from tubal sterilization stem from the method's effectiveness in preventing pregnancy.²²¹ Most complications from these methods exist at the time of surgery. For a couple deciding on sterilization, it should be noted that the health risk is lower for the man to have a vasectomy than for the woman to have a tubal ligation.²²² PID in women who have been sterilized is said to be 0.2 percent compared to 2 percent in a control group, not because of the procedure itself but because of different patterns of sexual behaviour in this self-selected group of women.

(b) Vasectomy

Vasectomy or male sterilization involves cutting and sealing the vas deferens, the tube that carries sperm from the testes, so sperm will not be present in ejaculate. The failure rate is less than 1 percent. A vasectomy is a simple procedure that usually takes place in the physician's office or outpatient clinic under local anaesthesia. Any complications are almost always minor and of brief duration (swelling, discoloration, or discomfort). Vasectomy should be considered a permanent contraceptive method. A reversal may be possible, but surgery is costly and success cannot be guaranteed. Pollowing microsurgical reversal of a vasectomy, pregnancy rates of 30-70 percent have been reported, provided the procedure is carried out within five to seven years of the initial procedure and the female partner is fertile.

Contraception should be practised for at least three months following vasectomy. Semen samples must be obtained 12-16 weeks apart to ensure there are no sperm and the operation is successful. Secondary anastomosis, resulting in contraceptive failure, is rare but has been reported. 226

Vasectomy achieves permanent infertility with the least possible disruption of daily life, at low cost, and without hospitalization. It causes no significant harmful health effects. When performed on mature, well-informed men, it has no adverse psychological repercussions. The operation carries minimal morbidity and no mortality when done under aseptic conditions using local anaesthesia. There is no alteration of sexual activity or hormones and no evidence of increased cardiovascular, endocrine, or autoimmune disease or neoplasia (cancer).

Contraceptive Use and Sexually Transmitted Diseases

Sexually Transmitted Diseases

STDs are among the most common public health problems. They are associated with pelvic infection, pelvic pain, and subsequent infertility. Some individuals are infected repeatedly and may have more than one infection simultaneously. 227

STDs can have serious short- and long-term health consequences. For example, a woman with chlamydia or gonorrhoea may develop PID, which may result in ectopic pregnancy and future infertility. Some STDs (e.g., syphilis) may increase the risk of spontaneous abortion, stillbirth, or premature birth. 228 STDS may be transmitted to a woman's offspring during pregnancy or childbirth, causing infant pneumonia, blindness, mental retardation, or death. 229

Individuals with certain STDs may transmit the infection for many years. They may suffer chronic disability or develop cancer as a consequence of the infection. They may die from other effects of the STD, such as human papillomavirus.²³⁰

Persons at risk of acquiring STDs are those who have had sex with someone who had other partners, or who have multiple partners. For example, two-thirds of all sexually active women aged 15-44 have had sex with more than one partner. Many individuals have experienced successive long-term, monogamous relationships (referred to as serial monogamy); however, many women and men have had more than one partner in a short period either because they move among short-term relationships or because they are simultaneously involved with more than one person. 232

Women who change sexual partners risk having intercourse with someone with STDs. Women appear to be more likely than men to acquire STDs following a single act of heterosexual intercourse with an infected person. Repeated sexual contact with the same infected person poses an even greater risk of disease transmission for men and women.

Preventing Sexually Transmitted Diseases

Contraceptives can alter the likelihood of infection. When used correctly and for every act of intercourse, condoms can markedly reduce the transmission of bacterial STDs and provide some protection against viruses such as HIV and those causing genital herpes and genital warts.²³⁴ Inconsistent condom use offers little protection.

The diaphragm also provides some protection against bacterial STDs, especially when used with a spermicide. In laboratory tests, spermicides kill organisms responsible for gonorrhoea, chlamydia, and several viral infections, including HIV.

Studies of women at high risk of contracting STDs show that spermicide used with the sponge helps reduce incidence of those infections. Similarly, a condom used with a spermicide may be more effective at preventing STD transmission than the condom alone among men and women.

Other contraceptive methods, including periodic abstinence, withdrawal, sterilization, IUDs, oral contraceptives, and other hormonal methods, offer no protection against vaginal and cervical infections. While the pill aids in preventing the spread of infection into the upper genital tract by its effect on cervical mucus, the risk of STDs remains.

Lower genital tract infections with vaginal bacteria (trichomonas and perhaps also gonorrhoea) appear more common among women using birth control pills than among non-users, but it is unclear whether the pill alters a woman's likelihood of infection or whether the increased incidence of infection is due to increased sexual activity. On the other hand, evidence suggests that the pill protects against symptomatic upper genital tract infection, one of the consequences of STDs. 236

Upper Genital Tract Infection

PID develops if an infection spreads into a woman's upper genital tract, uterus, fallopian tubes, ovaries, or peritoneum. Ten to 15 percent of gonorrhoea sufferers will get PID if the initial infection is untreated. ²³⁷ Various birth control methods have different effects on the probability of developing an upper genital tract infection. A method can modify a woman's chances of becoming infected with a STD and, independently, change the likelihood of developing PID if she does contract a disease. Contraceptive methods with high failure rates mean those pregnancies resulting have the usual risk of PID as a consequence of the pregnancy.

PID and upper genital tract infection appear among about 1 percent of sexually active women yearly, usually as a consequence of STDs. Upper genital tract infection also may develop after childbirth or abortion, if a woman has contracted a disease before or during the pregnancy.²³⁸

In its worst form, PID is an acute illness whose symptoms are pain and fever; however, the disease often is so mild that affected women do not recognize it. Periodically, it may flare up and cause chronic pain and ill health.²³⁹ Even in its mild form, PID can cause permanent scarring of the fallopian tubes or peritoneum, which may lead to ectopic pregnancy or tubal infertility. It is probably likely to be "silent" if it is caused by

chlamydia.

Women in mutually monogamous relationships are unlikely to contract STDs and thus are unlikely to contract an upper genital tract infection. Women with multiple partners or whose partners have had multiple partners are at high risk for STDs. Among such women, use of barrier and spermicidal methods or oral contraceptives will prevent many upper genital tract infections;²⁴⁰ using periodic abstinence, the IUD, or no birth control method will add substantially to the risk of infection.²⁴¹

Barrier and spermicidal methods reduce the incidence of PIDs to about half of that experienced by women using no birth control. Mechanical barrier and spermicidal methods used in combination are effective in reducing the incidence of PID. Oral contraceptives can also reduce the incidence of PID and subsequent infertility. A possible explanation is that the thickened mucus that develops in users of such contraceptives acts as a barrier to ascending infection. Tubal sterilization also is thought to reduce the risk of PID.

IUDs increase the chance of developing PID. Upon IUD insertion, cervical or vaginal, micro-organisms may enter the uterus. 245 In the first month after insertion, the IUD wearer is about four times more likely to develop PID than a woman using no birth control. The risk decreases quickly with time. 246

Women in mutually monogamous relationships who use barrier and spermicidal methods, oral contraceptives, or tubal sterilization are estimated to have at least 100 fewer annual episodes of upper genital tract infection per 100 000 than mutually monogamous women using no method and giving birth. The absolute benefits of these methods are even greater for women in non-monogamous relationships. ²⁴⁸

Periodic abstinence does not increase the risk of upper genital tract infection among women in mutually monogamous relationships; however, the method gives no protection against PID. Among women whose relationships are not mutually monogamous, the net result is that, compared with those using no contraceptives and giving birth, users of periodic abstinence have 1 300 more episodes of upper genital tract infection per 100 000 annually. This is because those using periodic abstinence spend more time not pregnant in which they are susceptible to an ascending infection from STDs. Compared to their counterparts using oral contraceptives and barrier and spermicidal methods, they will have a greater risk of PID.

Women who use no birth control and those who terminate a pregnancy with abortion are at higher risk of upper genital tract infection than those giving birth. This is not because abortion increases the risk of upper genital tract infection, but because women who use no birth control or undergo abortion spend less time pregnant than women who carry a

pregnancy to term. Thus, these women face the negative health risks associated with not using birth control.

Overall, it is reasonable to assume that choosing oral contraceptives or barrier and spermicidal methods instead of long-acting hormonal methods, progesterone-bearing IUDs, or vasectomy might help in preventing PID. Further data are needed. 250

Ectopic Pregnancy

More than 1 percent of all pregnancies are ectopic.²⁵¹ Many are the consequence of previous tubal infection. Use of any birth control method reduces the risk of ectopic pregnancy relative to that associated with use of no birth control. This benefit is most pronounced among women in mutually monogamous relationships. Pregnancies resulting from the failure of certain contraceptive methods are more likely to be ectopic than those resulting from the failure of others.

An ectopic pregnancy results when a fertilized egg implants itself outside the uterus, usually in the fallopian tube. An undetected ectopic pregnancy may rupture the fallopian tube, leading to severe bleeding and a potentially life-threatening emergency. The risk of ectopic pregnancy is increased among women who have had STDs, PID, a previous ectopic pregnancy, or tubal or pelvic surgery to treat infertility. Such women are more likely to have damaged fallopian tubes.

Among women using contraceptives, the probability of ectopic pregnancy depends on four factors: the method's effectiveness at preventing pregnancy; the method's effect on the risk of ectopic pregnancy, in case of contraceptive failure; the woman's likelihood of becoming infected with STDs; and the method's influence on the likelihood of developing upper genital tract infection.

If a woman chooses to abort an unplanned pregnancy rather than carry it to term, the risk that her next pregnancy will be ectopic may be reduced. This is because the risk of upper genital tract infection (a cause of ectopic pregnancy) is lower after induced abortion than after childbirth. Over time, however, a woman using no birth control and choosing to terminate the pregnancies by abortion would have a greater risk of ectopic pregnancy than a woman who uses no birth control and gives birth. The reason for this is that women who choose abortion could become pregnant again and be at risk from ectopic pregnancy within a short time, while women giving birth would be protected against further pregnancies (and further ectopic pregnancies) during the months they are pregnant and for a short time thereafter.

Aiding in the prevention of ectopic pregnancy is a benefit of all birth control methods. The benefit is greatest for women in non-monogamous relationships because of their higher risk of STDs and tubal infection. Use of birth control prevents an estimated 30-280 ectopic pregnancies annually per 100 000 women in mutually monogamous relationships. This

compares to prevention of an estimated 680-920 ectopic pregnancies annually per 100 000 women in non-monogamous relationships.²⁵⁸

Striking differences emerge in the incidence of ectopic pregnancies among women relying on tubal sterilization and vasectomy. In the rare event of pregnancy, the chance that it will be ectopic is not affected by vasectomy but is high among women who have undergone tubal sterilization. Nevertheless, because of the low risk of contraceptive failure, 100 000 women who have undergone tubal ligation can be expected to experience fewer ectopic pregnancies than an equal number of women using no contraception.

The incidence of ectopic pregnancy differs little among women in monogamous or non-monogamous relationships who use long-acting hormonal methods, tubal sterilization, or IUDs. This is because the

likelihood that any of these women will become pregnant is low.

Tubal Infertility

Upper genital tract infection and ectopic pregnancy can lead to tubal infertility; thus, birth control methods and other factors that change the risk of infection or ectopic pregnancy can affect the risk of infertility. Women in non-monogamous relationships or those in which a partner carries STDs are at increased risk of tubal infertility, especially if they use an IUD, periodic abstinence, or no method of contraception. Barrier and spermicidal methods will help to preserve these women's potential to bear children. Women in mutually monogamous relationships in which neither partner has a STD have a lower risk of tubal infertility. Contraceptive choices will have little influence on their future fertility.

About 85 percent of women having unprotected intercourse can expect to conceive within a year. After two years, the likelihood of conception falls to about 1-3 percent per cycle. Chance may explain why some women do not conceive when having unprotected intercourse; however, the longer the elapsed time, the greater the likelihood that the couple is infertile.

The older the woman, the more likely that she or her partner is infertile. One reason is that a woman is more likely to acquire infections over time that lead to blockage of the fallopian tubes. Couples using contraceptives may not know whether they are fertile or infertile until they try to conceive, and a woman's reproductive life is limited. By the late 30s and 40s, a woman's menstrual cycle typically becomes less regular and ovulation is less frequent. When an older woman does become pregnant, the chance of spontaneous abortion also is increased.

Infertility may result from factors concerning the man (about 25 percent of couples), the woman (35 percent), or both partners (24 percent), or it may be unexplained (16 percent). Among women, a common cause of infertility is blocked fallopian tubes. PID and other upper genital tract infections are common causes of this tubal infertility. Ectopic pregnancy and pelvic surgery, such as appendectomy or surgery for

treatment of ovarian cysts, are other associated factors.²⁶⁴ Because use of contraceptives influences the likelihood of upper genital tract infection and ectopic pregnancy, it indirectly affects the chance of developing tubal infertility.

There is no indication that any birth control method causes tubal infertility directly. Tubal infertility is much more common among women at high risk of infection than among those at low risk (those in non-monogamous relationships versus those in monogamous relationships). The likelihood of developing tubal infertility is low among women in mutually monogamous relationships in which neither partner has a STD.

In mutually monogamous relationships, women using no birth control are most likely to become infertile by developing blocked fallopian tubes. One incident of abortion is no more likely to be followed by tubal infertility than is one birth. ²⁶⁵ But if a woman were to use no contraceptives over five years and terminate all pregnancies by abortion, she could expect a higher likelihood of tubal infertility than if she were to give birth. This is because she probably would conceive more often and thus have more opportunities for ectopic pregnancies and upper genital tract infection. All contraceptive methods help to prevent tubal infertility among women in mutually monogamous relationships. The IUD offers the least protection against tubal infertility, but the difference between it and other methods is small among women in mutually monogamous relationships. ²⁶⁶

By contrast, choice of contraceptive has a substantial effect on the likelihood of developing tubal infertility among women in non-monogamous relationships. Compared with those using no method, users of barrier and spermicidal methods will have a lower incidence of tubal infertility. Oral contraceptives also will prevent tubal infertility, although to a lesser degree than barrier and spermicidal methods. Compared with users of the pill and barrier and spermicidal methods, women relying on periodic abstinence are at greatly increased risk of tubal infertility if they are in a non-monogamous relationship. Those relying on periodic abstinence will experience more cases of tubal infertility over five years than women who use no contraceptives and give birth. This is because they are likely to have had more cases of PID.

Likewise, the IUD is a poor choice for women in non-monogamous relationships. Because such women are at higher risk of contracting STDs and upper genital tract infections, use of the IUD adds greatly to the risk of tubal infertility. IUD users in mutually monogamous relationships will not be protected from upper genital tract infection to the same extent as users of barrier and spermicidal methods or oral contraceptives; however, they will be less likely to experience tubal infertility than those using no birth control. It is a poor choice for women in non-monogamous relationships.

Strategies for Prevention of Infertility Related to STDs by Appropriate Choice of Contraceptives

Behavioural Approaches

Introduction

There are two fundamental factors that may act independently or may interact to affect contraceptive-related infertility. First, human factors may contribute to infertility, beyond the contribution of any contraceptives used. Such factors include the individual's sexual behaviour (e.g., monogamous or non-monogamous), the individual's contraceptive behaviour (e.g., consistency of contraceptive use; barrier or non-barrier method), and the health care provider's behaviour (e.g., prescription of a contraceptive that is appropriate for the individual, more or less likely to be used, and more or less likely to protect the individual against STDs, upper genital tract infection, and infertility).

Second, contraceptive-related factors may contribute to infertility. Such factors include the inherent safety or risk of the method relative to fertility; the barrier or non-barrier nature of the method; the method's relative effectiveness; and the relative acceptability of the method to the user.

It must be emphasized that human factors and contraceptive-related factors usually interact in complex fashion. For example, when factors such as non-monogamous behaviour and use of the IUD are present, the combined effect sharply increases the IUD wearer's risk of contraceptive-related infertility. In more complex fashion, when factors such as non-monogamous behaviour and use of oral contraceptives are present, the pill user's overall risk of STD infection is increased. Specifically, however, the likelihood that a chlamydia infection will enter the upper genital tract is increased, but the likelihood that a gonococcal infection will reach the upper genital tract is decreased. The net interactive effect of these factors on contraceptive-related infertility is a function of the likelihood of contracting each STD and of the likelihood of its ascent into the upper genital tract.

Human Factors and Contraceptive-Related Infertility

Clearly, human factors contribute significantly to the occurrence of contraceptive-related infertility. Thus, prevention strategies that aim to modify users' sexual and contraceptive behaviour and health care providers' practice behaviour may help reduce contraceptive-related infertility.

Psychological Determinants of Behaviour

The volume of conceptual and empirical studies concerning the psychological factors that promote reproductive health-related practices

such as contraceptive behaviour, STD preventive behaviour, and HIV/AIDS (acquired immunodeficiency syndrome) preventive behaviour are limited. Thus, the following sections should be considered speculative. They are based upon the recently proposed Information — Motivation — Behavioural Skills (IMB) Model of Reproductive Health Behaviour, which will be applied to understanding and modifying behaviour that contributes to infertility.

According to the IMB model, three factors that determine reproductive health behaviour may influence infertility. First, people need information about reproductive health problems that may affect fertility — and information about how to avoid such problems — if they are to practise behaviour that promotes reproductive health. Such information must be easy to understand and must be recognizable by the individual as "here's what I need to do to safeguard my own reproductive health." Second, people must be motivated to practise behaviour that promotes reproductive health. This motivation will be based on the individual's feelings about sexuality, his or her attitudes toward the particular reproductive health behaviour, his or her perceptions of the social acceptability of that behaviour, and his or her feelings of personal vulnerability to negative health outcomes if the behaviour is not practised. Third, even knowledgeable, well-motivated people need appropriate skills to practise behaviour that promotes reproductive health.

The IMB model suggests that information and motivation trigger the behavioural skills needed to initiate and maintain behaviour that promotes reproductive health. Information and motivation may also affect reproductive health behaviour directly, especially when behaviour that promotes reproductive health has no psychological cost to the individual and does not demand new or complicated skills. The IMB model has been confirmed empirically in two U.S. studies of the determinants of AIDS-preventive behaviour conducted among male and female university students and among gay men.²⁷³ In both studies, AIDS prevention information and motivation were related to AIDS prevention behavioural skills, and these skills were related to the practice of behaviour to prevent AIDS.

The IMB model is consistent with interventions aimed at the prevention of pregnancy, STDs, and the transmission of HIV/AIDS. 274 Only when these interventions focussed on all three critical components of the IMB model were they able to achieve impact upon pregnancy rates, condom use, and reduction of unsafe sexual practices. 275

Reproductive Health Information and Behaviour

The IMB model holds that reproductive health information that is easy to understand, learn, and put into personal practice may help reduce the risk of infertility. Today, most Canadian adolescents and adults possess information concerning sexual activity that is easy to understand, learn,

and translate into behaviour. Unfortunately, some people have learned and

adopted misinformation that increases their risk of infertility.

It may be assumed that most adolescents and adults have access to the plentiful existing information about the mechanics of sexual intercourse. Most of these individuals possess enough information to avoid pregnancy (widely perceived as the major inhibitor of and negative consequence of sexual activity). 276 At the same time, however, many of these people are uninformed about the relationship between unintended pregnancy, abortion, and secondary infertility. Many are unaware of the links between STDs and impaired fertility. Many do not know whether the chosen contraceptive prevents STDs as well as pregnancy and they do not know about the potential consequences of these infections. Many believe that STDs are a problem only for non-monogamous "high-risk" persons not for themselves.²⁷⁷ Critically, many sexually active persons misperceive themselves as monogamous, when they actually engage in serial monogamy or have a partner who has done so. In that case, the risk of STDs and attendant infertility may still resemble that of an individual who has several sexual partners within a given period. 278 This mistaken self-perception may prompt individuals to feel invulnerable to STDs and to the need for STD-preventive behaviour that could preserve their fertility.

Individual Contraceptive Behaviour

Most sexually active Canadians possess information about effective means of contraception. Most people eventually act on this information, obtaining and using an effective contraceptive. Probably because Canadians know about effective contraceptives but lack information about STDs, infertility, and the relationship of contraceptives to prevention of STDs, many sexually active Canadians opt for oral contraceptives rather than barrier methods, thus increasing their risk of STDs and the possibility of infertility. Probably because

The Behaviour of Health Care Providers

For purposes of this paper, it is assumed that providers of health care may offer well-intentioned yet incomplete information, thus elevating the public's risk of infertility because a method of contraception that protects against STDs as well as pregnancy is not chosen. In particular, providers of health care may misperceive their sexually active clients as monogamous individuals at low risk of STDs and infertility, primarily needing effective contraceptives. In reality, however, many of these clients may be serially monogamous persons at relatively high risk of STDs and infertility, needing both effective contraceptives and STD protection.

For example, a recent Canadian study of the contraceptive and STD experiences of first-year college and university women found that those with greater numbers of partners were most likely to have been prescribed oral contraceptives. They also were most likely to have already had a diagnosed STD, and they were least likely to be using condoms.²⁸¹

Motivation and Behaviour Patterns

For purposes of this paper, it is assumed that individuals and providers of health care essentially are motivated to behave in ways that inadvertently promote infertility because a method not protecting against STDs is used rather than a method that would protect reproductive health and fertility.

Individual Sexual Behaviour

More than a decade of research has established that while many people are sufficiently accepting of their own sexuality to permit them to engage in intercourse, many of them also are too anxious to prepare for intercourse by taking precautions (e.g., discussing STDs with a prospective partner or buying and using condoms) that would tend to preserve their fertility. Studies have found repeatedly that sexually active individuals have relatively positive attitudes toward intercourse, but they have relatively negative attitudes toward the reproductive health behaviours (e.g., discussing STD prevention with a partner, engaging in sexually pleasurable activities that stop short of intercourse, or buying and using condoms) that would also help preserve their fertility. State of the state of the

Through the media and personal contacts, older adolescents and adults gain support and acceptance for their sexual activity; however, overt social support for the consistent practice of behaviour that promotes reproductive health and preserves fertility is lacking. Few people perceive themselves to be vulnerable to STDs and infertility or to unplanned pregnancy and the associated risk of secondary infertility. The reason for this is that there is little accurate information available about the incidence of such events, and individuals tend to underestimate the likelihood that such events will happen to them.²⁸⁴ Even when STDs or related fertility-threatening events occur, they are unlikely to be made public. This further contributes to the perception that "these things can't/won't happen to me."

Individual Contraceptive Behaviour

Many sexually active persons are motivated to use contraceptives that do not protect against STDs. They tend to eschew methods such as condoms or diaphragms that might act to preserve fertility. In terms of sexual anxiety, the use of oral contraceptives may be much less costly in emotional terms than is the donning of a condom or use of a diaphragm. Oral contraceptives may be less likely to provoke guilt, but they are far more likely to elevate the risk of infertility by way of exposure to STDs and the possibility of ascending upper genital tract infection.

Individuals often have a more positive attitude toward oral contraceptives, because they are effective, are non-intrusive, and may be used without regard to the timing of coitus, than they have toward barrier methods, which are less effective at preventing pregnancy and more intrusive than oral contraceptives. Such attitudes, however, also mean contraceptives are used that tend indirectly to elevate the risk of infertility. Use of oral contraceptives is often viewed as the normative, normal "thing

to do." On the other hand, the use of condoms is often viewed with suspicion ("Why do you *need* to use a condom?") and may stigmatize a person as a risky partner. Many individuals view pregnancy as the worst likely outcome of their sexual activity and thus are highly motivated to use the most effective contraceptive available. At the same time, because they view STDs and infertility as unlikely, they are poorly motivated to avoid such outcomes.

The Behaviour of Health Care Providers

For purposes of this paper, it is assumed that providers of health care hold feelings, attitudes, norms, and perceptions of client vulnerability similar to those of the general population, and that these incline them toward inadvertently acting to increase the public's risk of infertility by suggesting a contraceptive that does not protect against STDs. For example, the providers of health care may have sex-related anxieties that prevent them from accurately assessing clients' sexual behaviour patterns and preventive needs. These anxieties may make it easier for some providers of health care to prescribe oral contraceptives than to talk with a client about how to use a barrier contraceptive or how to fit a diaphragm. ²⁸⁶

Professional socialization may encourage some providers of health care to favour highly effective contraceptives (e.g., oral contraceptives or IUDs) over less effective methods (e.g., condoms or diaphragms). This also may cause them to favour the use of drugs over the use of devices, even though the former methods pose more risk of infertility than the latter. Providers of health care may view the prescription of oral contraceptives to sexually active clients as normative and likely to be well accepted by clients. On the other hand, they may view encouragement to use a barrier method as non-normative, likely to be rejected by clients, and likely to be seen as suggesting that clients are promiscuous. These perceptions may be accurate; however, they have the result of favouring the promotion of methods that do not protect against STDs, but just protect against pregnancy, and thus lead to greater incidence of fertility as a consequence.

Finally, providers of health care may well share with their clients the misperception that their clients are monogamous when they practise serial monogamy (at considerable risk of STDs and infertility). Such perceptions of monogamy and risk would result in inappropriate prescribing behaviour.

Behavioural Skills and Behaviour

Currently, most people's behavioural skills favour the creation of opportunities for sexual contact, but they provide little basis for the practice of behaviour to preserve fertility. It appears that individuals and providers of health care lack important behavioural skills related to reproductive health. This contributes to the occurrence of infertility that could be avoided.

Individual Sexual Behaviour

Most adults possess patterns of species- and culture-specific proceptive behaviour that attract the attention and erotic interest of potential sexual partners.²⁸⁷ In Western culture, sexual activity often occurs without overt verbal acknowledgment of the partner's sexual objectives, within the context of a seduction scenario, or while under the influence of drugs or alcohol. The combination of these factors may create occasions for sexual contact, but they are inimical to the practice of previously mentioned behaviour that promotes reproductive health and preserves fertility.

The practice of behaviour that promotes reproductive health and tends to protect fertility requires complex intra- and interpersonal skills. 288 First, an individual must accept that he or she is sexually active and, thus, must consider his or her reproductive health. Such self-admission is often difficult. Second, the individual must set a personal reproductive health agenda. This may include priorities such as avoiding pregnancy and/or STDs. The agenda should mesh with the individual's other social and sexual priorities. Third, the individual must possess the skills to negotiate his or her agenda in pre-sex discussion with a potential sexual partner. This too may be challenging, since most individuals have had little opportunity to practise such behaviour, and the partner may try to undermine the individual's reproductive health agenda. At this point, the partners may need to discuss limiting sexual contact to non-intercourse activities, using barrier contraceptives, seeking STD testing, or agreeing to remain monogamous. As a result, individuals must know how to exit situations or relationships in which their reproductive health concerns are not respected.

Fourth, assuming that the partners have agreed on a mutual reproductive health agenda, the individual must actively seek contraceptive counselling, purchase condoms, or seek STD testing. In addition, the individual must initiate a pattern of reproductive health behaviour that will be maintained consistently over time. Thus, he or she must learn how to reinforce the partner's motivation for practising this important behaviour. Finally, the individual must possess skills for reviewing the quality of his or her reproductive health practices and making changes if necessary.

Individual Contraceptive Behaviour

Generally, individuals' behavioural skills now tend to make likely the occurrence of unprotected intercourse or use of non-barrier contraceptives, posing risk to the individual's fertility that could be avoided. It has been observed repeatedly that individuals who are emotionally ambivalent about their sexual activity find it difficult to initiate and maintain contraceptive use. Despite the inability of oral contraceptives to protect against STDs, their popularity may be explained in a number of ways. For example, the use of oral contraceptives does not require an individual to discuss

contraception with a partner, purchase a sexual device, or manipulate the genitals to apply or insert the device.

The Behaviour of Health Care Providers

Many providers of health care lack the behavioural skills needed to educate clients about sexual behaviour and attendant threats to fertility, to identify clients who require barrier contraceptives, or to negotiate the use of such precautions with them. As a result, their actions may unintentionally serve to place their clients' fertility at unnecessary risk. To educate clients about fertility risks, to detect behaviour that might signal the need for vigilance about fertility, or to prescribe a barrier contraceptive, the provider of health care has to engage in behaviour that is relatively complicated, potentially costly in emotional terms, and most likely unfamiliar.

First, the provider of health care must accept the client's sexual activity without rendering moral judgment. Second, he or she must skilfully take a client sexual history, sensitive to serial monogamy and other threats to fertility, as a precursor to appropriate contraceptive counselling and decision making to safeguard fertility. Third, he or she must voice personal views of appropriate reproductive health behaviour with the client, who may be strongly motivated to disagree with the professional. He or she must use logic, compassion, and authority in negotiating appropriate reproductive health practices with the client. Finally, assuming that agreement has been reached with the client, the provider of health care must reinforce and support the client's efforts to maintain long-term practices that promote reproductive health, and must establish himself or herself as a consultant on this issue.

Reducing Contraceptive-Related Infertility

According to the IMB model, existing patterns of reproductive health information, motivation, and behavioural skills contribute to the occurrence of infertility that could be avoided by appropriate contraceptive choice. At the same time, however, the model holds that it should be possible to alter these and thus reduce the occurrence of such infertility. In this section, a prevention program directed at altering the information, motivation, and behavioural skills of individuals and providers of health care is proposed.

Changing Information, Motivation, and Behavioural Skills

In addition to its focus on modifying reproductive health information, motivation, and behavioural skills to promote reproductive health, the IMB model specifies a set of general operations that may be used to create and evaluate reproductive health interventions targeted at specific needs. The model's problem-solving approach consists of three elements:

1. The Elicitation Phase: Individuals within the target group are studied to determine what reproductive health information is

- lacking, their motivational obstacles, and necessary behavioural skills.
- 2. The Intervention Phase: Specific interventions are created and delivered to remedy information gaps, motivational obstacles, and skill deficits found to be important causes of contraceptive-related infertility in the previous phase.
- 3. The Evaluation Phase: Changes in the target group's reproductive health information, motivation, behavioural skills, and behaviour are assessed to determine what direct and indirect measures have been taken by group members over the short and long term. Then, the intervention is evaluated and refined as necessary.

Reducing Risk Associated with Individual Sexual Behaviour

Based upon available information, it would seem critical to inform sexually active Canadians about the incidence, transmission, prevention, and consequences for fertility of STDs. Equally important is to inform them that many individuals who believe themselves monogamous actually practise serial monogamy, which poses considerable risk of STDs and may endanger fertility. Such information is relatively easy to convey through print or broadcast media targeted to a particular audience. Presumably, such information would help reduce the individual's exposure to threats to infertility caused by his or her own uninformed sexual behaviour.

Reducing Risk Associated with Individual Contraceptive Behaviour

Similarly, it would seem important to inform sexually active Canadians about the implications of non-contraceptive intercourse and various contraceptive methods for fertility. It appears that sexually active Canadians are ill informed of the implications of non-contraceptive intercourse and unintended pregnancy, birth, and abortion for fertility; they are poorly informed about the prevalence of STDs that may threaten their fertility; and they are insufficiently informed about the implications of their chosen contraceptive for risk of STDs and infertility. Again, such information could be provided relatively easily through media aimed at the target group. Such information would act to reduce the occurrence of infertility that could be avoided by the individual's contraceptive behaviour.

Changing the Behaviour of Health Care Providers

Research indicates that oral contraceptives are routinely prescribed to young Canadian women with multiple partners. Predictably, many of these women experience STDs and a threat to their fertility. Providers of health care may be insufficiently sensitive to the fertility implications of prescribed contraceptives. Such information gaps, and others that may emerge with research, are related to the unintentional infertility that results from choice of contraceptives that do not protect against STDs. Again, such information gaps may be relatively easily filled through professional and continuing education, drug advertising, and other appropriate information

channels. This information may help to reduce the inadvertent contribution by providers of health care to infertility that could be prevented.

Changing Motivation for Individual Sexual Behaviour

To motivate individuals to modify their sexual behaviour so that it poses less risk to their fertility, it is necessary to change individuals' feelings about sexuality, their attitudes toward various behaviours, their perceptions of the social acceptability of these behaviours, and their perceptions of their own vulnerability to infertility should they fail to take protective measures. Highlighting the benefits to the individual of practising behaviour that promotes reproductive health can help modify attitudes toward such behaviour and encourage its performance. At the same time, educational messages that feature individuals like those in the target audience who endorse behaviour that promotes reproductive health can help identify such behaviour as desirable and "in," thus encouraging its performance.

Changing Individual Contraceptive Behaviour

Individuals must be helped to overcome any sexual anxiety surrounding the use of barrier contraceptives. Educational materials that portray similar individuals who use barrier contraceptives with assurance, and who can integrate them into foreplay, may help to change attitudes. The messages should highlight the relevant personal benefits of contraceptives that preserve fertility and the relevant costs of sole reliance on contraceptives that do not protect fertility. In this fashion, changing attitudes may result in changing behaviour, with less risk of infertility.

Changing the Behaviour of Health Care Providers

Ongoing education must focus on portraying providers of health care as professionals who comfortably advise clients about reproductive health matters. At the same time, these messages should show clients accepting practices that promote reproductive health. This may help providers of health care to develop the emotional equanimity necessary for acceptable practice. Educational efforts should also inform providers of health care about the unintended impact of prescribed contraceptives and that it is inappropriate to protect only against pregnancy in situations that are nonmonogamous. Both pregnancy and STDs must be protected against. This may help modify attitudes in a direction that will lessen users' risk of infertility. Conveying to providers of health care that professional norms are changing, and that they also may want to help their clients change their own norms, could result in a greater perception of the social acceptance of such actions among providers of health care. Educating the providers of health care about their clients' vulnerability to risks may also prove helpful in motivating them to promote behaviour that poses less risk to their clients' fertility.

Changing Individual Reproductive Health Behavioural Skills

For an individual to engage in sexual practices that tend to preserve fertility, he or she must perform a complex behavioural "script" seldom mastered and rarely taught. It follows that teaching, modelling, rehearsing, and refining performance of this series of behavioural skills would be a major step in reducing contraceptive-related infertility. First, individuals must accept that they are sexually active and must consider prevention issues. Educators might help to accomplish this (1) by accepting the legitimacy of responsible sexual behaviour; (2) by stressing that sexual activity itself is normal and to be expected; and (3) by emphasizing that refusing to acknowledge one's sexual activity is a prescription for reproductive health disaster.

Second, individuals must be taught to formulate a personal reproductive health agenda. They must possess information about threats to reproductive health and how to avoid them. Then they must have the opportunity to integrate this information into their own fabric of social and sexual priorities to achieve these objectives while preserving their reproductive health. Third, individuals must be able to observe successful models for raising and negotiating their reproductive health agendas with others, for dealing with partner resistance, and for leaving situations or relationships that threaten their reproductive health. They must have the opportunity to practise these skills through role play, thus enabling them to assert preventive behaviour in their own lives. They must also be able to observe and, if possible, to practise public behaviour, such as buying condoms, or visiting a STD clinic, that may be important to their future fertility. Finally, they must come to enjoy the self-assurance that will come with practising behaviour that preserves fertility.

Fourth, sexually active individuals must reinforce their partners for cooperating with and supporting their own reproductive health agenda. They must be encouraged to review the reproductive health outcomes experienced and, if necessary, to modify their reproductive health practices. Standard modelling, role playing, assertiveness training, and related techniques are available for teaching such behavioural skills and have been used successfully in modifying sex-related behaviour.²⁹¹

Evaluating Changes in the Behaviour of Individuals and Health Care Providers

Following the elicitation and intervention phases of the process, research will be needed to determine whether the intervention has changed the levels of information, motivation, and behavioural skills among individuals and providers of health care. Research will also determine whether and to what degree such changes have affected infertility and the factors that may contribute to it.

Ideally, the three-phase process — comprising elicitation, intervention, and evaluation — would encompass comparison treatment groups of sexually active individuals and their providers of health care. Each group

would receive interventions based upon specifically identified information gaps, motivational obstacles, and lack of behavioural skills believed to contribute to infertility that could be avoided by choice of appropriate contraception. Following informational programs, subjects would be evaluated for indicators of infertility risk. Conditions that might lead to infertility in the short and long term would be evaluated. For example, self-reports of condom use and reviewing of medical records for the evaluation process would include monitoring information concerning contraceptive choices; occurrence of STDs, unwanted pregnancies, births, and abortions; and long-term infertility problems.

Currently, the literature contains no description of a comprehensive intervention designed to reduce infertility factors and infertility; however, evidence suggests that such intervention would be effective. For example, interventions that focussed on STD and HIV/AIDS prevention information, motivation, and behavioural skills resulted in significant modifications in the condom use and risky sexual behaviour of STD clinic patients, gay men, homeless street youth, and minority youth. Further, a multi-year, campus-wide saturation campaign involving lectures and print and video media emphasizing contraceptive use information, motivation, and behavioural skills appears to have produced a dramatic, rapid reduction in the pregnancy rate at a major Canadian university. ²⁹³

Future Contraceptive Research

Five major objectives can be identified for efforts to improve contraceptives: they should be available for men as well as women, and ideally they should be more effective for those who wish to prevent or postpone childbearing; the side-effects associated with today's most effective methods should be reduced; methods that are more acceptable to people who now do not use contraceptives should be found; contraceptives that do not delay return to fertility should be found; and contraceptives that reduce the risk of pelvic infection and thereby reduce the threat to fertility should be developed.

It is possible to look ahead 10-15 years to anticipate new contraceptives or major modifications to existing contraceptives. Some things on the horizon are as follows:

• Implant contraception entails introducing progesterone in small silastic (capsule) tubes beneath the skin. The method provides long-term contraceptive effect without action on the user's part, except for the initial placement and eventual removal. The Norplant system is an effective, safe, and reversible method of long-term contraception. One clinic visit can replace three to five years of daily pill taking. Norplant implants can be removed at any time. Studies have established that fertility occurs at a normal rate after removal. 294 The growth and developmental patterns of babies born to women who stopped using the

implants to get pregnant have been found to be normal.²⁹⁵ In related research, biodegradable implants are replacing silastic tubes as the carrier for contraceptive progestin.²⁹⁶

- Advances in the biology of cell receptors have progressed rapidly in recent years. The first of this new class of progesterone antagonists to be tested for its effect on pregnancy is Mifepristone® (RU-486). The addition of prostaglandins enhances its effectiveness for preventing pregnancy.²⁹⁷ When women take RU-486 tablets orally for one to three days, the progestational support of the endometrium is interrupted and menstrual bleeding ensues. If this occurs in a month when fertilization has occurred, the fertilized egg or early embryo is discharged with the menstrual flow. The sooner RU-486 is taken after the first missed period, the more effective it is in terminating the pregnancy. Such menses-inducing therapy is an important alternative to surgical termination of early pregnancy. In future, products consisting of other progestin antagonists and some form of prostaglandin will be available in many countries, helping to curtail worldwide maternal mortality resulting from illicit abortions.
- Using natural estrogen, scientists are developing contraceptives based on the ability of the vaginal epithelium to absorb steroids. Such contraceptives eliminate daily pill taking and are delivered through a contraceptive vaginal ring, moulded into a silastic ring about the size of a diaphragm. The ring is disposable and changed every 21 days. The level of contraceptives in the user's blood is about the same as that of oral contraceptive users, and the pregnancy rates of both groups are similar.
- Several fertility-regulating (anti-pregnancy) vaccines are in clinical trial. They interfere with the action of the human pregnancy hormone (chorionic gonadotropin, or hCG). The hCG-based anti-fertility vaccine is well along in the developmental process, but it will be several years before information on its basic effectiveness, immunization schedule, reversibility, and side-effects is known.
- Among current new contraceptive approaches, the most extensive clinical experience has been accumulated concerning daily oral contraceptives taken by men. In the case of contraceptive use of Gossypoll, the yellow pigment found in the cotton seed, men took the drug daily for 60 days then switched to a less frequent maintenance dose. Initially, the drug was reported to be 99.4 percent effective in suppressing sperm count, but it was associated with a drop in blood potassium levels. It also was associated with a delay in the return of fertility among 80 percent

of users one year after discontinuation, and some men remained infertile for several years. Nonetheless, research related to appropriate dose and changes in the drug's structure still may make this a feasible male contraceptive in future.

In other research for male contraceptives, LH releasing hormone antagonists have been developed to suppress sperm counts, but results are unpredictable. These drugs may be delivered by injection or through a nasal spray, but absorption is variable. A long-acting subdermal implant also is being studied. Future prospects for male contraceptives will depend on greater understanding of male reproduction. The movement of sperm outside the testicles may be susceptible to controlled interference — for example, through the suppression of FSH by Inhibin, which can be produced by gene technology. The physical role of Inhibin and how it could be used in birth control are subjects for research.

In summary, contraceptive methods have changed significantly since the introduction of the pill and the modern IUD more than 25 years ago. Research continues on ways to make all barrier, oral, surgical, and hormonal methods easier and more effective to use, with less risk to the user. Clinical research trials are in progress that could add substantially to the array of choices: new female contraceptive implants; a contragestational drug that prevents the establishment or maintenance of early pregnancy; a vaccine to prevent pregnancy without interfering with normal menstruation; a male pill to prevent sperm formation or motility without impairing libido; and, perhaps, a male contraceptive injection or implant. New methods are likely to be effective in reducing the risk of pregnancy, reversible, and less likely to impair fertility or have any long-term adverse effects on pregnancy.

Conclusions and Recommendations

Two-thirds of Canadian women are now of childbearing age. Almost 500 000 pregnancies were reported in 1986. Many of these pregnancies were unintended, which contributed significantly to the 66 120 therapeutic abortions performed that year in Canada. The social, economic, and health consequences of the lack of fertility control have a major impact on the lives of individual women and on the status of women in general.

Teenage pregnancy is a particularly serious health and social issue, facing one in six adolescent girls under age 20. Statistics show that 26 percent of Grade 9 students and almost half of Grade 11 students have had sexual intercourse, yet most sexually active teenagers do not use contraceptives regularly. The spread of STDs is a growing problem in Canada, with consequences including reduced fertility, permanent sterility, and death. Infertility is a serious reproductive problem, affecting 8 percent

of couples of reproductive age.²⁹⁹ Many new cases of infertility result as a consequence of STDs and are preventable.

In spite of the serious, costly consequences of unintended pregnancy and the spread of STDs, many Canadians cannot obtain the most basic health services needed to prevent sexual and reproductive health problems. Access to quality services is especially restricted among individuals in rural and isolated areas, adolescents, single adult women, members of cultural and linguistic minority groups, physically handicapped individuals, and others with distinct health and socioeconomic needs.

Research demonstrates that provision of health care services and education clearly reduces the incidence of unintended pregnancy and STDs among women; however, services and funding in these areas are being reduced.

Future Policies in Canada Regarding Reproductive Health

Based on the information provided in this paper, we have identified several areas that we feel need action and policy to be implemented. They are listed below.

- The federal government should use its spending power and enforce standards of the Canada Health Act to ensure universal access to services that promote sexual and reproductive health for Canadians.
- 2. The federal government should develop a long-term financing strategy for programs based on a disease prevention/health promotion model, replacing its current curative approach to reproductive and sexual health.
- 3. The federal government should support and undertake research related to the diverse sexual health needs and reproductive health needs of Canadian women, youth, cultural and linguistic minorities, physically and mentally challenged individuals, and others with distinct needs.
- 4. The federal government should improve the content, quality, and timing of delivery of federal programs that address prevention of STDs and unplanned pregnancy.
- 5. The federal government should promote and use a comprehensive decision-making model rather than simply teaching abstinence in sexual matters, and should promote programs that highlight the use of decisions and behaviours that preserve reproductive health and fertility.
- 6. Professionals and the public should be educated that the concomitant use of two contraceptive systems (dual protection) is necessary for both pregnancy control and the prevention of infection-based infertility. There is a need for public and professional education regarding the expert use of contraceptives with a view to protecting

- against unwanted pregnancy and an equal concern for future reproductive health.
- 7. The media have a responsibility to play a more positive role in the promotion of health protection conferred by highly effective contraceptives.
- 8. Both federal and provincial governments must share the responsibility with industry in furthering research into newer, more effective, and safer contraceptives, as well as addressing the education, promotion, and delivery of services in pregnancy and STD prevention.

Notes

- 1. Canadian Fertility Survey conducted in 1984.
- 2. Royal College of General Practitioners, Oral Contraceptives and Health: An Interim Report from the Oral Contraception Study of the Royal College of General Practitioners (London: Pitman Publishing, 1974); and Royal College of General Practitioners' Oral Contraception Study, "The Outcome of Pregnancy in Former Oral Contraceptive Users," British Journal of Obstetrics and Gynaecology 83 (1976): 608-16.
- 3. H.W. Ory, J.D. Forrest, and R. Lincoln, *Making Choices: Evaluating the Health Risks and Benefits of Birth Control Methods* (New York: Alan Guttmacher Institute, 1983).
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The Physiological Links Between Endometriosis and Infertility: Review of the Medical Literature and Annotated Bibliography (1985-1990)

Arlyss Ponchuk



Executive Summary

Endometriosis is a disease primarily of women in their reproductive years. Tissue similar to the womb's lining (the endometrium) locates outside the womb, in the pelvic cavity. This misplaced tissue can be activated during menstruation by hormones, but unlike menstrual flow its effects remain trapped in the body.

Moderate or severe endometriosis can produce anatomic distortions, scarring, or endometriomas that are associated with decreased fertility. The relationship between minimal or mild endometriosis and infertility, however, is still a matter of controversy. Mechanisms induced by or associated with endometriosis that are not immediately visible might cause infertility even with minimal or mild endometriosis. Medical investigators conducting clinical studies assume this is the case, and examine specific ovarian deficiencies and biochemical possibilities in a quest for the links. However, reviewers of papers published on these studies agree that none of the findings demonstrate conclusively a specific relationship between minimal and mild endometriosis and

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infertility. The relationship between endometriosis and infertility may not be one of cause and effect. Perhaps an as yet unknown third factor causes infertility in women with endometriosis. The issue is important, and more research is appropriate.

Introduction

Endometriosis is one of the more mystifying diseases that medical practitioners face today. It is perhaps the most common disease treated by gynaecologists, yet neither cause nor cure is known. Although cases have been reported in men, endometriosis affects primarily women. The disease is found most frequently in the area of a woman's reproductive system. While women more often seek treatment for pain, infertility is also a significant issue.

Medical researchers accept as a rough statistical standard that approximately 30 percent of women with endometriosis experience infertility. The influence of endometriosis on fertility is plausible in cases where the disease is severe enough to produce damage visible at surgery. But can endometriosis in its minimal and mild stages interfere with fertility?

With the expectation that more is happening at the microscopic level than meets the eye at surgery, researchers have brought to bear the tools of modern technology to examine reproductive cycle processes and biochemical activities in infertile women with endometriosis.

The technology needed to study the human body at a biochemical level became available only in approximately the last 20 years. The 1970s and 1980s saw a surge of research into the relationship between minimal/mild endometriosis and infertility, with focuses on a wide range of reproductive cycle processes and biochemical issues. The range is so wide that medical reviewers who have attempted to summarize studies to date have presented the information in varying formats.

The structure chosen for this report is designed to accomplish two ends: first, to introduce the reader gradually to the terms and concepts and inter-relations of matters pertaining to clinical studies in endometriosis-related infertility; and second, to present the findings of clinical studies in a way that leads logically from one concept to the next, and that enables each concept to shed a light on other concepts discussed. The human body is a flux of interactive processes. This report's representation of physiological functions should clarify the influences and activities, and make sense of the flux. But because so much remains yet to be ascertained about unknown variables, what is here presented can be perceived only as a framework for future research to fill with new discoveries.

Medical researchers in this subject area tend to agree that there is likely a relationship between minimal/mild endometriosis and infertility. It is suggested that it is probable that specific relationships will be

discovered that will aid in the treatment of endometriosis-related infertility. This report aims to present for the first time this highly technical subject in terms understandable to the layperson as well as the medical professional.

Methodology

This research project began as an annotated bibliography of clinical studies on endometriosis-related infertility published since 1985. The mid-1980s was chosen as a starting point because the 1980s saw a surge in research into endometriosis, and by mid-decade some significant myths about the disease had been dispelled.

Searches on the medical data bases MEDLINE and Excerpta Medica for the period between 1985 and 1990 produced approximately 300 articles per year on a variety of subjects pertaining to endometriosis and infertility. These can be sub-categorized as

- physiological malfunctions within peritoneal fluid and within the larger structures of the reproductive system;
- 2. environmental influences the issues faced by the individual in coping with endometriosis-related infertility; and
- 3. treatments such as surgery, hormonal therapy, and assisted fertility.

As a result of the wealth of information available on endometriosisrelated infertility, the study was narrowed down specifically to an examination of the physiological links between endometriosis and infertility.

The biochemical and reproductive studies located for this specialized subject require an intensive knowledge of highly technical concepts and terms. Because the research compiled for the Royal Commission is intended to be read by both professionals and the public, an introductory section was added (Part 1) to precede the annotated bibliography (Part 2).

Part 1 begins with a general essay entitled "Endometriosis," which sets in a larger context the issue of physiological links between endometriosis and infertility. This introductory essay is followed by an essay specifically on the physiological links between endometriosis and infertility, which summarizes the relevant medical research to date and introduces the reader to terms, relevant physiological processes, theories, and drawbacks to studies. Part 1 addresses only the physiological factors discussed in medical literature, not the scientific tools and techniques used to carry out the clinical studies. Part 1 closes with a glossary intended to be used primarily in conjunction with the essay on "The Physiological Links Between Endometriosis and Infertility" of Part 1. But the Glossary might also be of use directly with the "Annotated Bibliography" of Part 2.

Part 2, the "Annotated Bibliography," begins with a section of 14 published reviews of the medical literature — summaries of all findings to date and similar to, but more technically worded than, the review provided in Part 1 of this report. The remainder of the "Annotated Bibliography" consists of 79 published articles on clinical studies — scientifically controlled enquiries into specific issues, conducted either in laboratories or in hospital treatment centres.

The "Reviews" section serves several purposes. Because the subsequent "Clinical Studies" section includes only those clinical studies published in the period between 1985 and 1990, and because some issues were studied in depth prior to 1985, "Clinical Studies" subsections occasionally include fewer entries than Part 1 would suggest. Moreover, because of the cut-off date of 1985, the "Clinical Studies" section will not necessarily include the most authoritative articles on a given subject. The "Reviews" section offers the reader technically detailed information on the breadth of research into the subject over the years preceding as well as following 1985, from the varying points of view of 10 medical researchers. Used in conjunction with Part 1, the "Reviews" section in Part 2 can help the reader place the annotated entries of the "Clinical Studies" section into context.

The "Clinical Studies" section employs the same subheadings as the review essay in Part 1 on "The Physiological Links Between Endometriosis and Infertility." The reader can compare information in the essay and bibliography for each subsection.

A full methodology for Part 2, the "Annotated Bibliography," is provided at the beginning of that section, and should be read carefully prior to making use of the annotated bibliography.

Part 1. Review of the Medical Literature

Endometriosis

Endometriosis is a chronic disease primarily of women in their reproductive years. Tissue similar to that which lines the womb locates outside the womb in the pelvic cavity or, less frequently, in other parts of the body. The hormones that trigger the womb's endometrium to generate tissue and to bleed menstrually can also stimulate these misplaced tissues, causing a response that differs somewhat from that of the womb's lining. Unlike normal endometrial secretions that exit the body via menstruation, the tissue and secretions of endometriosis remain trapped in the body, causing internal inflammation, formation of cysts and scar tissues, occasional bleeding, and related medical problems.

In a 1990 survey of 618 Canadian women, Kerbel Health Care Group found that only half the women interviewed were aware of the medical

condition called endometriosis. Of this half, more than a quarter knew little or nothing about the disease other than its name.

The cause of endometriosis is unknown. Most medical researchers agree that retrograde menstruation probably contributes to endometriosis in at least some cases. Retrograde menstruation is the backflow of menstrual blood, containing endometrial cells, from the uterus through the fallopian tubes and into the pelvic cavity. Once in the pelvic cavity, the displaced endometrial tissues might attach and grow. Healthy women with retrograde menstruation would not develop endometriosis if, from one menstrual flow to the next, their bodies cleaned away the menstrual debris accumulating in the pelvic cavity.

The theory of retrograde menstruation was first posited well over 50 years ago by John A. Sampson (1927), who coined the term "endometriosis" to describe this disease. While Sampson's theory has been popularly accepted as plausible up to the current day, studies have not proven initial attachment of transplanted cells in the manner he describes.

Perhaps endometriosis is hereditary, or congenital. The immune system might also play a role in promoting endometriosis, although the potential exact mechanism is still being researched. In some cases, endometrial tissue might inadvertently be transported by surgeons during pelvic surgery for other conditions. Endometriosis might also be caused by the transportation of endometrial cells through the lymphatic or blood circulatory systems. Very little is known about endometriosis; very much is theorized.

Neither the prevalence nor the incidence of endometriosis can be determined to the satisfaction of medical researchers. The prevalence of a disease is the percentage of persons with the disease (new plus old cases) in a population at a particular time. Medical researchers estimate that as many as 20 percent of all women, and from 10 percent to 40 percent of women with infertility, have endometriosis. It is estimated that 30 percent to 50 percent of women with endometriosis are subfertile. Positive diagnosis of endometriosis is based on the presence of ectopic (out-of-place) endometrial tissue, regardless of where the tissue is located or whether or not it interferes with bodily functions. Not all women seek medical intervention for the disease. Many women believe that their pain is a normal part of the menstrual cycle; others experience no pain or inconvenience at all. On occasion endometriosis is diagnosed only when a woman undergoes pelvic surgery for an infertility work-up or for another medical reason. Medical reviewers suggest that the true prevalence of women with endometriosis, and of women with endometriosis and infertility, will remain unknown until a non-invasive screening test is developed for use on the general population.

The incidence of a disease is the percentage of new cases that appear in a healthy population exposed to the risk in a certain unit of time (e.g., one year). In 1991, Dr. Giovanni Battista Candiani of Milan, Italy, and his colleagues calculated an incidence rate for endometriosis based on

statistics at non-federal hospitals in the United States in 1980. They found that approximately four women out of 1 000 in the age range of 15 to 64 years are hospitalized annually for endometriosis — a percentage slightly higher, according to Candiani, than that for breast cancer.

According to the Endometriosis Association (1992) based in Milwaukee, Wisconsin, an international support group with over 8 000 members, a woman with endometriosis tends to be diagnosed for the disease approximately 10 years after onset of the first symptoms. Physicians consider endometriosis as a possible diagnosis if a patient does not respond favourably to prior treatments for menstrual pain, general pelvic pain, pain with sexual intercourse, or infertility.

The only sure diagnosis of endometriosis is by visual contact with the disease site during surgery or, more exactly, by biopsy of suspected tissues at surgery. For biopsy, a tissue sample is surgically removed and then examined microscopically in the laboratory to attain positive identification.

For women with infertility, a surgeon can measure the extent of the disease at surgery, from minimal to severe, by filling in standardized charts produced by the American Fertility Society.

In 1979 the American Fertility Society created a classification system for endometriosis specifically to measure the extent to which the disease might affect conception. Revised in 1985, it has become the "industry standard" for clinical studies when they report endometriosis as minimal, mild, moderate, or severe.

But the Revised-American Fertility Society (R-AFS) system must be revised again for it to continue to be relevant. One of the criteria used in the system is the presence of "black" lesions indicating endometrial implants. However, in the last decade medical researchers have established that endometriosis can appear not only in the classic colour of the black lesion, but also in colours ranging from clear to yellow, red, green, blue, and purple. Black lesions are now thought to represent old, inactive sites of endometriosis.

In the R-AFS system, disease severity is based primarily on the severity of pelvic scar tissue, since this is thought to have an impact on infertility. Ovarian endometriosis is also emphasized, since ovary function is crucial to fertility. Disease with a small lesion on an ovary may be rated more severe than disease with a large endometrioma elsewhere in the pelvic cavity. Accordingly, the system does not take into consideration extrapelvic endometriosis, such as endometriosis of the bowel.

Increasing micro-technology in the last decade has enabled medical researchers to consider the influence of microscopic endometrial implants and the molecular components of peritoneal fluid on reproductive processes. This too is not reflected in the R-AFS system.

Finally, the R-AFS system does not correlate a woman's level of pain with an appropriate categorization of her disease.

This last drawback is perhaps unfair to mention. The R-AFS system was designed specifically to categorize the effect of endometriosis on

infertility, not to measure the general extent of disease or to measure pain levels. But no comparable system exists to measure disabling effects other than infertility. The R-AFS system's widespread acceptance and use tie in neatly with the medical profession's longstanding tradition of measuring treatment success by post-treatment pregnancy rates. Most of the reasearch conducted on endometriosis concerns fertility, not pain relief.

Most women seek treatment for pain relief, not infertility. Only after strong advocacy efforts by the Endometriosis Association in the 1980s did medical researchers emphasize studies on pain relief. To date, however, no comparably accepted classification system exists to measure the extent of

endometriosis with reference to pain.

Perhaps in the recent past one reason for the failure to diagnose women for up to 10 years after the onset of their symptoms was that open abdominal surgery, *laparotomy*, was postponed until absolutely necessary. *Laparoscopy* (microsurgery through a laparoscope inserted in a tiny abdominal incision, sometimes called "keyhole surgery") is a technology recently applied to diagnosing and treating endometriosis. In *laser vaporization laparoscopy* a surgeon uses a laser to vaporize lesions, and in *laparoscopic excision* a surgeon uses a laser or small scissors to excise lesions.

As of spring 1992, no large-scale random controlled trials have been reported in the medical literature comparing the effectiveness of laser laparoscopic surgery or laparoscopic excision to laparotomy for treating endometriosis. A smattering of smaller studies tend to agree that laparoscopic surgery is as effective as laparotomy for treating endometriosis in less severe cases, but that neither is necessarily curative. Several studies have reported on what Anthony A. Luciano and colleagues call the "therapeutic, economic and social benefits" of laparoscopy in comparison These include a shorter hospital stay, a shorter to laparotomy. recuperation time, and a reduced need for post-operative painkillers. With laparoscopy, reduced bleeding, minimized damage to adjacent tissues, and reduction in abdominal scarring speed recovery, which in turn enables a woman to attempt to conceive sooner after surgery than a woman who has undergone laparotomy (Luciano et al. 1992; Azziz et al. 1989; Levine 1985; Steinberg 1991b).

In the last 20 years, the increasing use of laparoscopic surgery in the United States has enabled surgeons to diagnose and treat endometriosis at the minimal and mild stages more often. Before the advent of laparoscopy, endometriosis was considered a disease primarily of mature women between 30 and 40 years of age. Today more teenagers are being diagnosed. In a study conducted by Dr. Donald Goldstein of Boston, 52 percent of teenagers who underwent surgery for pelvic pain in his clinical practice were diagnosed as having endometriosis (Goldstein et al.

1980).

The Society of Obstetricians and Gynaecologists of Canada (SOGC) reported in the December 1990 issue of its journal that there are sufficient

resources for diagnosis and treatment of endometriosis in Canada so that travel out-of-country should not be necessary. Most of the article, however, addresses the need for more resources to treat women with endometriosis in Canada.

In Ontario, as of mid-1991, two laser laparoscopic centres were open in Ontario, one in London and one in Toronto, with one SOGC-certified surgeon at each. According to Dr. Wilfred Steinberg (1991a), a Toronto gynaecologist, "This needed treatment strategy is relatively unavailable in Ontario and in most other parts of Canada." Dr. George Vilos of London, Ontario, summarizes the difficulties: "expensive equipment" (a minimum of \$250 000 to \$500 000), "lack of trained personnel," "shortage of operating room time," and "shortage of outpatient facilities" (Vilos 1991, 58-59).

Dr. David Redwine of the St. Charles Medical Center in Bend, Oregon, has become recognized in North America for his use of laparoscopic excision with simple, inexpensive tools costing less than \$6 000 to treat women with endometriosis-associated pain. In 1991 Dr. Redwine reported on 10 years of laparoscopic excision for endometriosis in his practice. Of 359 patients, only 19 percent suffered persistent or recurrent disease at five years after surgery. He claims that 35 percent of his patients are Canadians unable to receive comparable treatment in Canada. Doctors from Alberta and Ontario have visited his clinic to observe his technique. To confirm if the technique does provide relief from pain, in 1991 Calgary's Foothills Hospital undertook a clinical trial on Dr. Redwine's technique, conducted by Dr. John Jarrell, head of obstetrics and gynaecology at Foothills Hospital and at the University of Calgary (Livingstone 1991).

As an alternative to surgery or in conjunction with surgery, physicians can prescribe hormonal drug therapy to suspend the menstrual cycle, usually for a period of six to nine months (i.e., no longer than a pregnancy). Without menstrual cycle hormones to stimulate them, some ectopic endometrial implants shrink for the duration of treatment. In the last five years, gonadotropin releasing hormone (Gn-RH) analogues have been overtaking Danazol[®] as the hormonal drug of choice prescribed by physicians. Gn-RH analogues are described as having more menopause-like but fewer masculinizing side-effects than Danazol[®].

However, the side-effects of each of these drugs vary widely from woman to woman. They can be severe enough in some women to induce them to stop treatment. In some cases, a woman is prescribed one drug and then another in a search for one that she can tolerate. Therefore, for the individual woman it cannot be said for certain in advance of treatment that any one of these drugs has fewer or less distressing side-effects than any of the other drugs.

Of the Gn-RH analogues, only Nafarelin (brand name Synarel[®]) has been approved by the Food and Administration Branch of Health and Welfare Canada for treatment of endometriosis in Canada. Other Gn-RH analogues currently prescribed by doctors in Canada are marketed under the names Lupron[®] and Zoladex[®].

A number of random controlled studies were conducted in the late 1980s on a variety of Gn-RH analogues, including Nafarelin (marketed in Canada as Synarel®), Buserelin, Lupron®, and Zoladex®. None has proven that medical therapy with the available hormonal drugs will eradicate endometriosis, provide long-term pain relief, or improve fertility.

Dr. Robert L. Barbieri, editor of The New England Journal of Medicine, reported in the edition of 25 February 1988 that a study headed by Dr. Milan R. Henzl, the results of which were published in that issue, was, in his opinion, "the best-designed and best-executed trial of drug therapy for endometriosis ever reported" (1988, 513). In the study, 213 patients with laparoscopically confirmed endometriosis were randomly assigned sixmonth treatment by Nafarelin (in nasal spray) or Danazol® (in tablets). Placebo nasal spray and placebo tablets provided double-blind comparison. Disease severity was rated by the American Fertility Society's scoring system in pre- and post-treatment laparoscopies. Results: "More than 80 percent of the patients in each treatment group had a reduction in the extent of disease as assessed by laparoscopy." Almost half of the study group had severe disease; by the end of the treatment period, their numbers "decreased from about 40 percent to 5 to 10 percent." And "of the 149 patients who tried to become pregnant, 58 (39 percent) succeeded after the completion of treatment; [but] similar rates of pregnancy applied to the three treatment groups" (Henzl et al. 1988, 485). Dr. Henzl and his colleagues did not discuss long-term follow-up in this report or in later reports (Barbieri 1988: Henzl et al. 1988).

In March 1992, the Nafarelin European Endometriosis Trial Group, on behalf of Syntex Research, reported on a randomized, double-blind, double-dummy clinical study in which 307 patients with laparoscopically diagnosed endometriosis received Nafarelin or Danazol® to determine the comparative effectiveness of each treatment. They found Nafarelin and Danazol® equally effective in reducing endometriosis growth and symptoms during treatment. Symptoms recurred in each group after treatment, but disease severity during a 12-month follow-up remained less than at the time of admission.

Gn-RH analogues can cause bone loss, which physicians believe might lead to osteoporosis later in a woman's life. Recent clinical studies are combining Gn-RH analogues with estrogen to reduce bone loss during treatment. The pharmaceutical company Syntex Inc. is, in 1992, funding clinical studies at a number of hospitals across Canada and the United States on combining the Gn-RH analogue Synarel® with estrogen add-back therapy.

Hormonal drug therapy can be prohibitively expensive for women who do not have access to prescription drug plans: the cost can run from one to several hundred dollars a month, depending on the prescription. To postpone surgery in cases of recurring endometriosis, physicians are known to prescribe repeated regimens of hormonal therapy. Long-term effects of

Danazol® and Gn-RH analogues (over five years) have not yet been established in clinical studies.

Current treatments other than laparoscopy and hormonal therapy include pain medications for pain management, laparotomy as a surgical alternative to laparoscopy, and hysterectomy as a last resort to decisively shut down the menstrual cycle. No cure is yet known. Even with surgical intervention, hormonal regimens, pregnancy, hysterectomy, or menopause, endometriosis can persist.

The Physiological Links Between Endometriosis and Infertility

Medical researchers agree that moderate to severe endometriosis can cause infertility by obvious means, such as anatomic distortions, endometriomas, and pelvic *adhesions*. Physicians advise women with moderate or severe endometriosis who want to become pregnant that their best chance is in the months after surgery or after ending hormonal drug therapy, before the endometrial implants have had time to regenerate.

Investigators are not so certain of the relationship between infertility and minimal or mild endometriosis — that is, endometriosis that does not cause visible obstructions to fertility. Clinical findings to date have been inconclusive; *in vitro* fertilization and expectant (wait-and-see) therapy have shown much the same fertility success rates in infertile women with minimal or mild endometriosis and infertile women without endometriosis.

Abnormalities in virtually every facet of the female reproductive process in infertile women with endometriosis have been proposed as "the cause" of their infertility. Medical researchers have found abnormalities in monthly cycle processes, and also in the biochemical components of peritoneal fluid (fluid within the pelvic cavity). The potential causes of minimal or mild endometriosis are legion, but none of those studied has stood out as a certain cause or even as the most probable cause. Instead, reviewers conclude that multiple co-existing mechanisms might impact on each other and, through additive effects unique to the individual woman, cumulate in endometriosis-associated infertility. To complicate matters, these mechanisms and their inter-relations vary not only from woman to woman but also within individual women from cycle to cycle. Given the wide range of variables for investigators to examine, research into this subject is as yet only preliminary, and findings are only tentative.

Even when multiple studies have been conducted on the same particular issue, results are difficult to compare because of the range of unstandardized criteria. Control groups vary from infertile women without endometriosis, to healthy women, to women with pelvic inflammatory disease (PID). Those women with endometriosis who are the subjects of research vary from women with minimal endometriosis to women with mild, moderate, or severe endometriosis, sometimes all in the same study. Many of the studies are based on a sample population of a few women, sometimes under 20 in number, with findings generalized to the population as a

whole. Investigators use various tools, such as laparoscopic equipment or ultrasonographic monitoring, and their findings vary according to the method employed. Some of the research to date has been done on animals, and results have been generalized to the human population. Despite the lack of definitive findings in single studies and the profusion of often uncomparable data, most reviewers and most investigators believe that the preliminary findings are promising enough to justify further, better coordinated research.

The following summary of medical research addresses the subject of the physiological links between minimal and mild endometriosis and infertility. In the first part, the five phases of a woman's normal monthly cycle are defined. Abnormalities found in three of the five phases in women with endometriosis are then presented. Included in this section are deficiencies particular to each phase, the possible relationship of endometriosis to infertility caused by the deficiencies, and drawbacks to the studies. The second part of the summary defines the cellular components of peritoneal fluid considered relevant to endometriosis-associated infertility. Like the first section, this section is subcategorized by definition of terms, details of findings, and drawbacks to the studies.

Reproductive Cycle Factors

For purposes of medical research, the monthly cycle of a woman's reproductive system is divided into five phases, based on an approximate 28-day cycle. The phases can overlap:

Menstrual Phase	Days 1 to 5
Follicular (or Proliferative) Phase	Days 6 to 12
Ovulatory Phase	Days 13 to 15
Luteal (or Secretory) Phase	Days 16 to 23
Premenstrual Phase	Days 24 to 28

Women are born with about one million eggs in their ovaries. Each egg (or ovum or oocyte) is surrounded by a single layer of cells called a follicle. In the follicular phase (approximately Day 6), one or more follicles are stimulated to mature. In the ovulatory phase (approximately Day 14), at ovulation, an egg is released from one or more follicles. An egg immediately passes into the nearby fallopian tube (or oviduct), moved into it by the sweeping motions of hair-like fimbriae at the ends of the oviducts, and then moved along the duct by the action of its lining. Meanwhile, the burst follicle collapses and forms into a collection of cells called the *corpus* luteum. In the luteal phase, the corpus luteum secretes a hormone to cause the lining (the endometrium) of the uterus to become thicker in preparation for receiving a fertilized egg. If by the premenstrual phase (approximately Day 24) a sperm has not fertilized the egg, the corpus luteum regresses and the egg exits the body with the unneeded endometrium via menstruation (on approximately Day 28, at commencement of the menstrual phase). The menstrual cycle then begins anew with

stimulation of another group of follicles. If, on the other hand, fertilization occurs, then the egg implants in the wall of the uterus, and the corpus luteum does not regress but continues to produce hormones.

Four hormones are primarily responsible for regulating the menstrual cycle: estrogen, progesterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH). The levels of the four rise and fall during the cycle in mutual stimulus and suppression. FSH promotes the growth of a group of follicles. Granulosa cells on the surface of the follicles have LH receptors, molecules designed to "grab" or attach to LH. The follicles secrete estrogen, primarily a type of estrogen called estradiol-17B. Estrogen volume peaks just before ovulation. By then, FSH has declined, and usually only one follicle, fed by FSH, has survived. The high level of estrogen secreted by all the follicles generates a surge in LH. This surge is limited to approximately 24 hours, long enough to cause the egg to burst from the follicle at the ovulatory phase.

Granulosa cell proliferation ceases after ovulation. The luteinizing cells now generate more progesterone than estrogen. Progesterone stimulates the endometrium to thicken. In the absence of fertilization, estrogen causes the corpus luteum to regress, bringing the luteal phase to an end. Estrogen and progesterone levels decline sharply; left unstimulated, two-thirds of the endometrium is shed in menstruation. If, on the other hand, an egg is successfully fertilized, luteal regression is prevented by the secretion of *human chorionic gonadotropin*. The corpus luteum continues to generate progesterone, which stimulates the endometrium's thickened lining, for maintenance of the pregnancy.

Follicular Phase Defects

Various studies have reported on follicular phase defects in women with endometriosis, including raised progesterone levels, premature follicular rupture, lower estradiol (estrogen) levels, reduced concentration of LH receptors in follicular tissue, decreased follicular growth rate and total growth period, and no follicular growth at all despite regular hormonal function.

Raised progesterone levels measured in infertile women with endometriosis suggest that a corpus luteum of the previous cycle failed to shrink and degenerate (a condition called *luteolysis*), but instead continues to produce progesterone until well into the current cycle. This could cause premature luteinization of the current developing follicle. The prematurely discharged egg would be too immature for successful fertilization.

Researchers have found reduced numbers of LH receptors in infertile women with endometriosis. Decreased FSH levels can reduce the growth of granulosa cells on the surface of the follicle, which in turn could reduce growth of the LH receptors on the surface of the granulosa cells. At midcycle, with fewer LH receptors, the follicle might be less sensitive to existing LH. This could result in failure of ovulation, defective corpus luteum formation, and other ovulatory dysfunctions, leading to infertility.

Studies documenting these findings are based on a small number of women, are inconclusive in their findings on the relationship between the follicular phase abnormality and an endometriosis/infertility relationship, and are unconfirmed by additional studies.

Ovulatory Phase Defects

Anovulation

Anovulation is the absence or suppression of ovulation. Several clinical studies have reported that anovulation is more common in women with mild endometriosis. Whether anovulation is a cause or effect of endometriosis has not been established.

Luteinized Unruptured Follicle (LUF) Syndrome

In the *luteinized unruptured follicle (LUF) syndrome*, an egg remains entrapped in the luteinized follicle or corpus luteum. Although the physical act of releasing the egg from the prepared follicle is prevented, doctors mistake the cycle for normal because other evidence of ovulation, including progesterone output, endometrium secretion, and basal body temperature, measure normal.

During laparoscopy or serial ultrasonic monitoring, physicians look for the LUF syndrome by examining the corpus luteum during the luteal phase for the presence of a stigma — the hole in the wall of the corpus luteum through which the egg was expelled. If the surface of the corpus luteum is intact, then no egg is likely to have burst forth, and the LUF syndrome is diagnosed.

The LUF syndrome is an attractive hypothesis to explain infertility in clinical situations such as minimal or mild endometriosis, where no other evident explanation exists. Accordingly, researchers have conducted clinical studies to determine the relation of the LUF syndrome with endometriosis and infertility.

Possible Involvement

Several clinical studies have reported that LUF syndrome is more common in women with mild endometriosis.

The LUF syndrome was first described in association with endometriosis by I.A. Brosens and colleagues in 1978. The LUF syndrome has been associated with low peritoneal fluid concentrations of progesterone and estradiol. Brosens and his colleagues posited that the naturally high progesterone content in peritoneal fluid of healthy women would inactivate misplaced endometrial cells. In women with the LUF syndrome, however, low levels of progesterone might allow free-floating endometrial cells to implant, resulting in endometriosis. Later studies by other researchers have reported variable results. Yet other researchers have proposed a reverse causality — that endometriosis might cause the LUF syndrome. Reviewers of the medical literature conclude for now that there is no clear association between endometriosis and the LUF syndrome.

Drawbacks to the Studies

The LUF syndrome would influence infertility only if it occurs repeatedly, in cycle after cycle. While at least one researcher claims that women with endometriosis have repeated LUF syndrome, others consider the syndrome to occur only sporadically.

The incidence of the LUF syndrome in infertile women with endometriosis varies greatly in clinical studies (from 13 percent to 83 percent of women studied, in samples ranging from 12 to 118 patients). Researchers suggest that more reliable and more comparable statistics could be derived from larger studies with examinations over more (six, for example) cycles.

Laparoscopy has been brought into question as a sound diagnostic tool for the LUF syndrome, since laparoscopic findings vary so greatly from investigator to investigator. Serial ultrasonic monitoring has produced more consistent study results, with incidences of the LUF syndrome tending to be consistently under 20 percent.

The LUF syndrome might occur with similar frequency in all women with infertility, not particularly in those infertile women with endometriosis.

Abnormal or High Prolactin Secretion

Prolactin is a hormone secreted by the pituitary gland that stimulates breast milk production in nursing mothers and supports gonadal function. Galactorrhoea refers to abnormal secretion of milk due to high prolactin; hyperprolactinaemia refers to high blood level of prolactin resulting from high secretion of prolactin. Researchers have associated hyperprolactinaemia with ovulatory dysfunction.

Some investigators have found higher incidence of galactorrhoea in infertile women with endometriosis. Other researchers have found that some infertile women with endometriosis have a greater capacity to secrete prolactin than healthy women. Some suggest that hyperprolactinaemia might cause endometriosis, which in turn might cause anovulation. Not all studies confirmed these findings.

There are no studies to support the idea that suppressing normal prolactin levels might alleviate endometriosis-related infertility. There is no conclusive evidence that prolactin levels are related to endometriosis and infertility.

Ovum Capture Inhibitor (OCI)

Researchers have theorized that a hypothetical *ovum capture inhibitor* (OCI) generated by endometriosis might interfere with the hairlike fimbria that capture the egg (ovum) as it bursts from the follicle at ovulation.

In a clinical study of golden hamsters published in 1988, Drs. H. Suginami and K. Yano exposed the hamsters to endometriotic peritoneal fluid. In the exposed hamsters and not in the controls, a membrane developed that completely covered the fimbria, interfering with ovum capture. After retrograde flushing, the membrane ballooned and detached from the fimbria, enabling the ovum capture process to resume

normal function. This might, in some cases, explain the observation that fertility increases after hysterosalpingography or after hydrotubation (Olive et al. 1985).

Luteal Phase Defects (LPD)

The term *luteal phase defects* covers a wide range of deficiencies that can occur in the luteal phase, particularly in relation to the corpus luteum.

In studies of the luteal phase in infertile women with endometriosis, researchers have found abnormal concentrations of estrogen and progesterone. Specific findings include delayed increase in production of progesterone or its metabolites, delayed decrease in estrogen levels after the pre-ovulatory peak, and biphasic mid-cycle LH surges. All studies with these findings have been contradicted by other studies that measured normal production.

Researchers have also measured reduced numbers of LH receptors, shorter luteal phases (under 10 days), and abnormal luteolysis in infertile women with endometriosis.

Drawbacks to the Studies

Luteal phase defects can occur in women with or without endometriosis, making it difficult to pinpoint those deficiencies specific to women with endometriosis.

Researchers now agree that accurate diagnosis of luteal phase deficiencies requires biopsies in the late luteal phase. Until recently, studies have published findings based on early, mid, and late luteal phases.

Peritoneal Fluid Factors

Peritoneal fluid is fluid contained in the pelvic cavity. It is named for the thin transparent membrane, called the *peritoneum*, that lines the abdominal cavity. The pelvic structures are continuously bathed in peritoneal fluid. Medical researchers believe that variations in the volume and content of this fluid might relate to the occurrence of endometriosis and the relationship between endometriosis and infertility.

Direct Toxicity of Peritoneal Fluid

Researchers have gathered evidence that the altered peritoneal environment of women with endometriosis might have a direct effect on sperm motility, sperm survival, sperm-egg interaction, embryo implantation, early embryonic development, and frequency of spontaneous abortion.

Sperm Function

Studies on the effect of peritoneal fluid on sperm have tended to show positive results that endometriosis might in a variety of ways impede sperm. More specific studies into sperm phagocytosis, discussed below under the section "Non-Specific Immunity," tend to indicate that an immune system altered by endometriosis may directly destroy sperm.

Embryo Implantation and Development

Research into mice and rabbits by researchers including R.N. Morcos and his colleagues (1985) and Do Won Hahn and his colleagues (1986) suggests that peritoneal fluid of women with endometriosis might be toxic to embryos or impede their implantation.

Spontaneous Abortion

Studies done in the 1960s and 1970s associated an increased frequency of spontaneous abortions with women who had endometriosis. More recently, J.D. Naples and his colleagues (1981), and J.M. Wheeler and his colleagues (1983), amongst other researchers, reaffirmed the relationship. But in a more rigorous study in 1986, D.A. Metzger and her colleagues used a well-defined control group to eliminate selection bias. These workers demonstrated that there is no significant difference in the spontaneous abortion rates of women with and without endometriosis. Several later researchers confirmed Metzger's findings. Peritoneal fluid toxicity is not addressed in the clinical studies as a cause of spontaneous abortion in women with endometriosis. It is, however, raised as a possibility in peer-assessed reviews of the medical literature.

To more carefully assess whether and why toxicity might occur,

researchers have attempted to isolate specific potential causes.

Peritoneal Fluid Volume

Dr. J.B. Maathuis and colleagues van Look and Michie were in 1978 among the first to observe that peritoneal fluid varies in volume predictably during the normal menstrual cycle, peaking in the luteal phase. Some clinical studies since then have found that women with endometriosis and "associated" infertility have increased peritoneal fluid volume throughout their cycle. Not all clinical studies have supported this finding.

Drawbacks to the Studies

Findings from various studies are difficult to compare since criteria varied from study to study. In some cases control groups consisted of normal fertile women, in other cases of subfertile women with pelvic adhesions. The phase of the cycle when peritoneal fluid was measured also varied.

Prostaglandins

Prostaglandins are one of a larger group of hormone-like chemicals called *prostanoids*. Prostaglandins are produced by multiple sources, including pelvic macrophages, endometrial implants, and the peritoneum itself. A potential role for prostaglandins has been found in almost every tissue of the body. Within the reproductive system, in the normal reproductive cycle, prostaglandins assist in pushing out the egg from the pre-ovulatory follicle, causing luteolysis, regulating tubal motility and ovum transport, and contracting the uterus. Within the immune response system, prostaglandins elicit inflammation.

Possible Involvement

Dr. S.I. Meldrum and his colleagues in 1977 were the first to report increased levels of prostanoids in the peritoneal fluid of women with mild endometriosis. In their study they found a greater than tenfold increase in prostaglandin F.

Since then, at least 15 clinical studies have been conducted on prostaglandin levels in the peritoneal fluid of women with endometriosis and infertility. The studies are evenly matched in their findings: approximately half confirm an increase in levels of prostaglandins, while the other half find no significant difference between their study and control groups.

There are numerous theories of how abnormal concentrations of prostaglandins in women with endometriosis might affect their fertility. For example, prostaglandins might reduce LH receptor levels in granulosa cells; interfere with the timing of the release of the egg from the pre-ovulatory follicle; cause the LUF syndrome; accelerate the movement of an egg through the fallopian tube, causing the embryo to arrive in the uterus at a less than optimal time for implantation; diminish corpus luteum function in humans, or cause premature luteolysis; and cause uterine contractions that could interfere with implantation or cause spontaneous abortion.

It is considered possible that endometrial implants increase prostanoid concentrations directly, and cause an inflammatory reaction that activates immune system constituents that, in turn, produce more prostaglandins. (Possible involvement of the immune response in endometriosis-related infertility is discussed below.)

Drawbacks to the Studies

Again, results from studies are difficult to compare, since criteria varied. Different studies extracted peritoneal fluid for analysis in different phases of the menstrual cycle. Sometimes the phase was documented, sometimes not. Because peritoneal fluid volume and cellular and chemical content vary during the cycle, timing of samples needs to be standardized before studies can be compared. Researchers recommend aspirating the fluid during the luteal phase, as the greatest amount of the prostanoid $PGF_{2\alpha}$ occurs during this phase.

Not all studies examined the same prostanoids; each chose one or several, including 6-keto- $F_{1\alpha}$, TxB_2 , PGE, PGE_2 , PGF, $PGF_{2\alpha}$, and $PGF_{2\alpha}$ metabolite. Therefore, although 15 or more clinical studies have been done on prostanoids, since few of the studies addressed the same types of prostaglandins, they do not lend themselves to comparison and confirmation.

Although most of the studies examined women with minimal or mild endometriosis, several included women with moderate or severe endometriosis. The control groups varied from study to study (for example, fertile or infertile women without endometriosis), and some were not well described. Some studies examined the peritoneal fluid only after centrifuging the fluid to remove other cellular components.

Study results might have been influenced by the care with which the aspirated fluid was measured and preserved. Peritoneal fluid for prostanoid measurement needs to be preserved immediately; any delay will alter findings because of the short half-life of some prostaglandins. The half-life of prostaglandins is anywhere from seconds to two or three minutes.

Immune Factors

The human body has a self-protective *immune system* that wards off and overcomes invading micro-organisms, or substances foreign to itself — *antigens*. Most often the various immune factors monitor the body in a non-activated state, but when faced with antigens they become activated. The immune system provides two distinct lines of defence, specific immunity and nonspecific immunity. Both might contribute to inflammation and an *autoimmune* response.

Inflammation and Autoimmune Response

Inflammation is a normal function of an immune response. But higher than normal levels of activated immune substances in peritoneal fluid might promote inflammation that could interfere with normal reproductive processes. Medical researchers theorize that immune factors might attack normal body cells (as a hyper- or autoimmune response) within women with minimal or mild endometriosis, resulting in a pelvic environment unfavourable to fertility. The ectopic (i.e., misplaced or "outside of the uterus") endometrial tissues of endometriosis might trigger an immune response. The *antibodies* triggered by the immune system to address the misplaced endometrial tissue might go on to attack endometrial tissues that are correctly located as uterine lining. This autoimmune reaction could interfere with normal reproductive processes.

Not all studies support this theory, however. Studies that used women with PID as their control group found the levels of auto-antibodies did not significantly differ between the women with endometriosis and the controls. Endometrial antibodies might occur in any instance of pelvic inflammation, not just in cases of endometriosis.

Drs. J.C. Weed and P.C. Arquembourg in 1980 were the first to detect an antibody to endometrial tissue in patients with endometriosis. Their findings were confirmed in 1982 by S. Mathur and his colleagues and in 1984 by S.Z. Badawy and his colleagues. However, antigens (i.e., original inflammatory stimuli) for the endometrial antibodies have not yet been isolated; researchers cannot be certain the cause of the increased concentrations is endometriosis. Moreover, findings conflict: researchers in other clinical studies have found no significant increase in endometrial auto-antibodies in women with endometriosis. Anti-ovarian auto-antibodies have also been reported in women with endometriosis.

Specific Immunity

Specific immunity is provided by white blood cells called lymphocytes. Lymphocytes originate in bone marrow. Those that remain in the bone marrow to mature are called B lymphocytes or B cells; those that travel to the thymus to mature are called T lymphocytes or T cells. Once mature, both B cells and T cells travel the blood circulatory and lymphatic systems to reside in tissues, there to monitor the body.

B cells generate antibodies that attach to antigens to neutralize them. Collectively, the antibodies produced by B cells are called *immunoglobulins*. There are five main classes of immunoglobulins: *IgG*, *IgM*, *IgA*, *IgD*, and *IgE*. The protection provided by B cells is called *humoral immunity* since the antibodies produced by the B cells identify and destroy antigens that are still circulating in the "humours," the bodily fluids of the blood circulatory and lymphatic systems.

T cells address antigens that have already invaded cells. For this reason, the protection provided by T cells is called *cell-mediated immunity*. Unlike B cells, T cells attack antigens directly, not via antibodies. T cells include *helper T cells* and *suppressor T cells*. Helper T cells generate proteins and other substances, collectively called *lymphokines*, to enhance the immune response. One function of lymphokines is to activate B cells to secrete immunoglobulins (i.e., antibodies). Helper T cells are themselves activated by *interleukin-1*, a protein secreted by *macrophages*, a type of scavenger cell (part of the non-specific immune system, described below). Interleukin-1 also stimulates production of prostaglandins and activates B cells to generate immunoglobulins.

A chain of 11 proteins called *complement* interacts catalytically to enhance the immune response — complement-1 triggers complement-2, which triggers complement-3, and so on. Complement proteins are produced by liver cells and by macrophages. Complement is activated most effectively by IgM and IgG antibodies, the most abundant classes of immunoglobulins. Like antibodies, complement proteins attach to the surface of antigens; these activated complement proteins attract scavenger cells that destroy the antigens by ingesting them.

The immune response occurs in waves of attack. Each of the immune factors of both specific and non-specific variety can immobilize, neutralize, or destroy some antigens; antigens that prove impermeable to such immune factors as antibodies, complement, T cells, and scavenger cells are disposed of by an as yet unclassified, and possibly non-specific, type of immune factor called *killer cells* (or *K cells*).

When defence is complete, suppressor T cells suppress, or deactivate, the activated immune system, placing it once again on standby to monitor the body.

Possible Involvement

In infertile women with minimal or mild endometriosis, researchers are finding higher than normal levels of immune system factors, including interleukin-1, complement-3, complement-4, and immunoglobulins. Higher concentrations of these various substances make the peritoneal fluid content of women with minimal or mild endometriosis significantly different from that of healthy women. Medical researchers conjecture that this altered peritoneal fluid environment has the potential to disrupt various aspects of the reproductive process, such as ovarian function, ovum pickup by fimbria (egg capture), sperm motility or survival, gamete interaction, tubal transport, or embryo growth. Research is preliminary in this area. In 1987 Dr. H. Fakih and his colleagues found that interleukin-1 in peritoneal fluid was toxic to the growth of two-cell mouse embryos *in vitro*.

Non-Specific Immunity

Unlike specific immune factors, non-specific, "unspecialized" immune cells can destroy all kinds of foreign microbes and cellular debris. Such scavenger cells are collectively called phagocytes (Greek for "eaters"). Macrophages, or mononuclear phagocytes, are literally the largest (macro) type of phagocyte (phage). Macrophages mature from cells called monocytes, which originate in bone marrow. Microphages (macrophages' smaller counterparts) are the first to arrive at an antigenic site, attracted by the microbes themselves, by damaged tissues, or, especially, by activated complement. Microphages ingest and destroy antigens and antibody-antigen complexes. Digestive enzymes released by microphages can cause local tissue damage. Slower to arrive to the site, monocytes and macrophages destroy larger antigens and clear away the damaged tissues and other remains.

The macrophage is the predominant cell type in the peritoneal fluid of healthy women, constituting approximately 90 percent of the *leukocytes* in the peritoneal cavity. Apart from their role as scavenger cells, macrophages contribute to normal body processes within the pelvic cavity. They might stimulate granulosa-luteal cell progesterone production, to contribute to the early survival of eggs or embryos. They might also regulate other, as yet unknown, activities within the pelvic cavity by release of catalytic products.

Within their role as scavenger cells, peritoneal macrophages might clear away the red blood cells of retrograde menstruation, which refers to menstrual blood that backflows up the fallopian tubes into the pelvic cavity — even in healthy women — and that, if not cleared, might result in endometriosis. Studies have found increased levels of macrophages in healthy women at the menstrual stage of their cycle, possibly activated to deal with retrograde menstrual flow. Macrophages might also eliminate any endometrial cells that migrate from the womb through the fallopian tubes and into the pelvic cavity. And macrophages might clear away damaged tissue fragments within the pelvic cavity that resulted from endometriosis.

Possible Involvement

Most studies agree that while healthy women have a higher count of peritoneal macrophages at menstruation, women with mild endometriosis have a high count throughout their monthly cycle. Women with endometriosis have also been found to have a higher level of macrophages in their fallopian tubes. Moreover, compared to the resident "inactivated" macrophage population in healthy women, the macrophages of women with mild endometriosis tend to be "activated."

According to the "macrophage theory," endometriosis triggers an inflammatory response that increases the number, concentration, or activation of the pelvic macrophages; these macrophages in turn decrease fertility by phagocytizing or damaging sperm, gametes, or embryos. Researchers have found that the activated macrophages in women with mild endometriosis demonstrate a higher frequency of *sperm phagocytosis* (damage or destruction of sperm by phagocytes). Moreover, activated phagocytes might secrete more enzymes and other macromolecules that might affect gamete movement, viability, fertilization, or development of the conceptus before or after implantation.

It is not known if the macrophage count is either a result or a cause of endometriosis. With the second possibility in mind, some researchers propose that the altered macrophage population might secrete products that promote growth of endometrial cells, rather than destroying them, in this way giving rise to endometriosis.

Researchers have not demonstrated with certainty any relationship between macrophage count and severity of disease. Neither have they ascertained that the higher macrophage count in women with endometriosis and infertility contributes to their infertility.

Drawbacks to the Studies

At least one clinical study has found that macrophages occur in higher numbers in women with infertility and no mechanical factor, a general class in which women with mild endometriosis constitute only one subset.

The clinical studies are difficult to compare, since they used different criteria: control groups consisted of infertile or fertile women without endometriosis, and peritoneal fluid was extracted in various stages of the reproductive cycle (the luteal phase is considered the best time). Some studies examined only women with mild disease; some studied women who had various stages of the disease, from mild to severe.

Tumour Necrosis Factor (TNF)

Tumour necrosis factor (TNF) is a product of activated monocytes, macrophages, and lymphocytes in response to inflammatory stimulants. TNF is cytotoxic toward gametes and has an adverse effect on sperm motility. Higher levels of TNF have been found in the peritoneal fluid of women with endometriosis than in the peritoneal fluid of healthy women. Investigators posit that the presence of TNF is associated with endometriosis and infertility.

Conclusion

The inter-relations of the reproductive hormones, the various cellular components of peritoneal fluid, and immune response factors are complex and not entirely understood. Research in this area is still at the frontier

stage.

Medical investigators have developed a general understanding of basic cellular activities within peritoneal fluid during the menstrual cycle, and they have ascertained that both the peritoneal fluid environment and the reproductive cycles of infertile women with endometriosis are dysfunctional in comparison to those of healthy women. However, as yet, investigators offer only suggestions for the cause of the defects, and for the specific relationship or relationships between minimal or mild endometriosis and infertility, projecting that future research will confirm or modify their theories.

Glossary

Note: Definitions of terms are based on their immediate relevance to the subject matter of endometriosis-related infertility. Some of the substances or factors defined have functions or implications wider than these selective definitions

suggest.

Core words, such as *Antibodies*, are represented in the glossary, but to prevent making a long glossary even longer, variations such as *Anti-Antibodies* or *Antisperm Antibodies* are not necessarily included. The meaning of the core word can be looked up — it may be modified by prefixes and suffixes. Abbreviations and alternate terms are included in the glossary, as they are not self-evident.

6-keto-F_{1\alpha}: One type of **prostaglandin (PG)**.

Adhesions: Scar tissue caused by the body's attempt to repair damage caused by inflammation, infection, disease, or surgery.

Anovulation: The absence of ovulation.

Antibodies: Proteins formed by **B cells** to eliminate invading micro-organisms. Antibodies have receptors that enable them to recognize specific **antigens** circulating in bodily fluids; they attach to the antigens and neutralize them.

Antigens: Molecules present on micro-organisms or other substances foreign to the body; are eliminated by **scavenger cells**, **antibodies**, **T cells**, and other productions of the body's **immune system**.

Autoimmunity: A disorder in which the body's immune responses become directed

against the body's own constituent parts.

B Cells (also called **B** lymphocytes): A type of lymphocyte that matures within bone marrow and then travels upon maturation into the blood and lymphatic circulatory systems. When triggered by antigens, B cells secrete antibodies, to provide the body with humoral immunity.

B Lymphocytes: See B cells. C3: See Complement-3.

C4: See Complement-4.

Cell-Mediated Immunity: The protection provided to the body by **T-cell** activation. Whereas the **antibodies** of **B cells** identify and destroy **antigens** that are still circulating, T cells identify and destroy antigens that have already invaded cells (thus, "cell-mediated immunity").

Complement: A chain of 11 proteins that interact catalytically to enhance the immune response (complement-1 triggers complement-2, which triggers complement-3, and so on). Complement proteins attach to **antigens** and either destroy them directly or attract **phagocytes** to the antigen site.

Complement-3 (also called C3): See Complement.

Complement-4 (also called C4): See Complement.

Corpus Luteum: A collection of cells formed from the collapse of a **follicle**, after an **egg** is released from the follicle. The corpus luteum secretes hormones (**estrogen**, and particularly **progesterone**) to thicken the lining of the uterus in preparation for a fertilized egg. If the egg is not fertilized, the corpus luteum shrinks and degenerates.

Ectopic: Out-of-place, or misplaced. In this publication, used in reference to ectopic endometrial tissue — tissue located not in the lining of the womb (**endometrium**) but outside the womb, elsewhere in the body, usually in the pelvic cavity — that gives rise to endometriosis.

Egg (also called **Ovum** or **Oocyte**): An unfertilized female egg, formed in an ovary. **Endometrium**: The lining of the womb. The endometrium is stimulated to thicken during a woman's monthly cycle, and approximately two-thirds is sloughed off in menstruation.

Estradiol-17B: The most common and potent form of estrogen.

Estrogen: One of the four hormones regulating the menstrual cycle. Estrogen volume peaks just before **ovulation**.

Fallopian Tube (also called **Oviduct**): The passage from the **ovary** to the uterus, through which an **egg** travels after it bursts from its **follicle**.

Fimbriae: Streamer-like membranes at the end of each **fallopian tube**, which help guide an **egg** from the **ovary** into the **oviduct** and toward the uterus.

Follicle: A structure composed of cells within the ovary, which surrounds an undeveloped **egg**. The egg at maturation bursts free from the follicle; the follicle then collapses and forms into a **corpus luteum**.

Follicle-Stimulating Hormone (abbreviated **FSH**): One of four hormones that regulate a woman's monthly cycle. FSH stimulates a group of follicles to mature during the **follicular phase**.

Follicular Phase (also called the **Proliferative Phase**): Approximately Days 6 to 12 of a woman's monthly reproductive cycle, when **follicle-stimulating hormone (FSH)** stimulates a group of **follicles** to mature.

FSH: Abbreviation for Follicle-Stimulating Hormone.

Galactorrhoea: Abnormal secretion of milk from the breasts. Usually a result of increased secretion of **prolactin**.

Granulocyte: Another name for Microphage or Polymorphonuclear Phagocyte. Granulosa Cells: Cells that multiply on the surface of follicles during the follicular phase. Granulosa cells develop LH receptors to enable the follicle to lock onto luteinizing hormone (LH) for the purpose of ovulation.

Helper T Cells (also called Helper T Lymphocytes): T cells activated by macrophages that have ingested antigens. Helper T cells secrete more immune response factors, collectively known as lymphokines.

Helper T Lymphocytes: See Helper T Cells.

Human Chorionic Gonadotropin: A hormone secreted by the placenta after an **egg** has been fertilized. This hormone maintains the **corpus luteum** until the placenta itself can secrete enough **progesterone** to sustain the pregnancy.

Humoral Immunity: The protection provided to the body by **B-cell** activation, so called since the **antibodies** produced by B cells circulate through the "humours" (bodily fluids of blood and lymph).

Hyperprolactinaemia: Excessive secretion of prolactin.

IgA: One class of immunoglobulins.
IgD: One class of immunoglobulins.
IgE: One class of immunoglobulins.

IgG: The most common class of immunoglobulins.

IgM: One class of immunoglobulins. IL-1: Abbreviation for Interleukin-1.

Immune System: The body's self-protective mechanism, which resists or overcomes invading micro-organisms that cause bodily damage.

Immunoglobulins (abbreviated Ig): The collective name for the antibodies produced by B cells. Immunoglobulins come in five main classes: IgG, IgM, IgA, IgD, and IgE.

Interleukin-1 (abbreviated IL-1): A protein secreted by activated macrophages. IL-1 activates T cells and B cells to provide the body with immunity against antigens.

In Vitro: A Latin term meaning literally "in glass." Refers to analysis or actualization of biological activities outside the body, in an "artificial" environment — usually in a petri dish or other laboratory vessel. See *In Vivo* for contrast.

In Vivo: A Latin term that refers to analysis or actualization of biological activities within the living body (as opposed to laboratory simulation). See In Vitro for contrast.

K Cells: Abbreviation for Killer Cells.

Killer (K) Cells: Cells different in structure but similar in function to **phagocytes** and **lymphocytes**, as a part of the **immune system** response.

Laparoscopic Excision: A type of **laparoscopy** (surgery) in which lesions of endometriosis are cut away with tiny scissors or laser. Contrast **Laser Vaporization Laparoscopy**.

Laparoscopy (also called "keyhole surgery"): A surgical procedure with general anaesthetic, in which a surgeon inserts a laparoscope (a thin telescope) into a small incision in the abdomen to perform microsurgery or to observe the interior organs of the body.

Laparotomy: Open abdominal surgery. See Laparoscopy for contrast.

Laser Vaporization Laparoscopy: A type of **laparoscopy** (surgery) in which lesions of endometriosis are evaporated by laser. Contrast **Laparoscopic Excision**.

Leukocytes: White blood corpuscles. **Microphages**, also known as **Granulocytes** or **Polymorphonuclear Phagocytes**, are one subset.

LH: Abbreviation for Luteinizing Hormone.

LUF Syndrome: Abbreviation for **Luteinized Unruptured Follicle Syndrome**. **Luteal Phase** (also called the **Secretory Phase**): Approximately Days 16 to 23 of a woman's monthly cycle, the period after **ovulation**, when an **egg** travels through

the **fallopian tube** to the uterus and when the **endometrium** generates a thicker lining in expectation that the egg will be fertilized and will implant.

Luteal Phase Deficiency: A range of disorders occurring in the **luteal phase** that can cause infertility by disrupting luteal phase activities.

Luteinized Unruptured Follicle (LUF) Syndrome: A condition in which an egg remains entrapped in the follicle or corpus luteum even after being stimulated by luteinizing hormone to burst free. The cycle is mistaken for normal by doctors because other evidence of ovulation, such as progesterone output, endometrium secretion, and basal body temperature, measure normal.

Luteinizing Hormone (abbreviated **LH**): One of the four hormones regulating a woman's monthly cycle. The **follicles** generate a surge of LH at approximately mid-cycle, which triggers **ovulation**.

Luteolysis: The regression or diminishing of the **corpus luteum** in the latter stages of the monthly cycle, if the **egg** has not been fertilized and implanted in the **endometrium**.

Lymphocytes: White blood cells, responsible for perceiving foreign substances. Lymphocytes travel the blood circulatory system and lymphatic system in an inactive state, until stimulated to action by foreign substances. There are two types of lymphocytes, **B cells** and **T cells**.

Lymphokines: **Immune system** response factor secreted by **helper T cells**, which in turn stimulate **B cells** to produce **antibodies**.

Macrophages (also called **Mononuclear Phagocytes**): Literally a large (macro) **phagocyte** (eater). Macrophages, like their smaller counterparts, **microphages**, are **scavenger cells** that engulf and destroy cellular debris and **antigens**. Macrophages originate in bone marrow as **monocytes**. Unlike microphages, macrophages can stimulate additional **immune system** responses to foreign micro-organisms.

Menstrual Phase: Approximately Days 1 to 5 of a woman's (approximately 28-day) monthly reproductive cycle, when an unfertilized **egg** and now-superfluous endometrial lining exit the body via menstruation.

Microphage (also called Polymorphonuclear Phagocyte, or Granulocyte): Literally a small (micro) phagocyte (eater). Microphages, like their larger counterparts, macrophages, are scavenger cells that engulf and destroy cellular debris and antigens.

Monocytes: Cells that originate in bone marrow, travel through the blood circulation, and mature into **macrophages**.

Mononuclear Phagocyte: See Macrophage. Natural Killer Cells: See Killer Cells.

OCI: Abbreviation for Ovum Capture Inhibitor.

Oocyte See Egg.

Ovaries: Paired female sex glands located at the tips of each **fallopian tube**. In the ovaries, **eggs** (within **follicles**) are developed and the hormones **estrogen** and **progesterone** are produced.

Oviduct: See Fallopian Tube.

Ovulation: The release of an **egg** from a **follicle** during the **ovulatory phase** of a woman's monthly cycle.

Ovulatory Phase (also called **Secretory Phase**): Approximately Days 13 to 15 of a woman's monthly cycle, when an **egg** is released from one **ovary**.

Ovum: See Egg.

Ovum Capture Inhibitor (OCI): Any obstruction that prevents an **egg** from passing from the **ovary** into the **fallopian tube** with the assistance of the **fimbriae**.

Peritoneal Fluid: Fluid contained in the pelvic cavity. It is named for the thin transparent membrane (called the **peritoneum**) that lines the abdominal cavity. The pelvic structures are continuously bathed in peritoneal fluid.

Peritoneum: A thin transparent membrane that lines the pelvic cavity to contain and protect the bodily organs.

PGE: One type of prostaglandin (PG).
PGF: One type of prostaglandin (PG).
PGF: One type of prostaglandin (PG).
PGF: One type of prostaglandin (PG).
PGF₂₀: One type of prostaglandin (PG).

PGF₂₀ Metabolite: One type of prostaglandin (PG).

Phagocytes (also called Scavenger Cells): The collective name for macrophages and microphages.

Phagocytosis: The act of engulfing, ingesting, and destroying, particularly by phagocytes.

Polymorphonuclear Phagocytes: See Leukocytes and Microphages.

Premenstrual Phase: Approximately Days 24 to 28 in a woman's monthly cycle, when fertilization of an egg has not occurred, and the reproductive system is preparing for menstruation.

Progesterone: One of the four hormones regulating a woman's monthly cycle. Progesterone levels are at their peak in the latter part of the cycle, secreted by the **corpus luteum** as a trigger for the **endometrium** to generate a thicker lining.

Prolactin: A hormone secreted by the pituitary gland. It stimulates breast milk production in nursing mothers and supports gonadal function.

Proliferative Phase: See Follicular Phase.

Prostaglandins (abbreviated **PG**): One class of **prostanoids**, produced by multiple sources, including pelvic **macrophages**, endometrial implants, and the **peritoneum**. A potential role for prostaglandins has been found in many tissues of the body. Within the reproductive system, prostaglandins help push the **egg** out from the preovulatory **follicle**, regress the **corpus luteum**, regulate tubal motility and **ovum** transport, and contract the uterus during menstruation. Within the **immune system** response, prostaglandins elicit inflammation.

Prostanoids: A hormone-like chemical. One subcategory is prostaglandins.

Receptors: Lock-and-key type mechanisms that enable one body to attract another (e.g., **LH** receptors on **granulosa cells**), which in turn enables a **follicle** to attach to **luteinizing hormone (LH)**.

Retrograde Menstruation: Backflow of menstrual blood up the fallopian tubes

into the pelvic cavity.

Scavenger Cells: Cells of the **immune system** that engulf, ingest, and destroy invading micro-organisms. See **phagocytes** for examples.

Secretory Phase: See Luteal Phase.

Sperm Phagocytosis: The damage or ingestion and destruction of sperm by phagocytes.

Stigma: The breach in the wall of the **corpus luteum** through which an **egg** has expelled itself from the **follicle** during **ovulation**. Absence of a stigma is a sign of the **LUF syndrome**.

T Cells (also called T Lymphocytes): A type of lymphocyte that originates in bone marrow but matures in the thymus. Upon maturation, T cells enter the

bloodstream and lymphatic system where they directly attack specific **antigens** to provide the body with **cell-mediated immunity**.

T Lymphocytes: See T Cells.

Tumour Necrosis Factor: A product of activated macrophages, monocytes, and lymphocytes, within an immune system response.

TxB₂: One type of prostaglandin.

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Part 2. Annotated Bibliography

Methodology

Publications included in this annotated bibliography were chosen by random selection based on a search of the medical data bases MEDLINE on CD-ROM under the headings "endometriosis" and "infertil" (1985-1990) and Excerpta Medica on CD-ROM under the headings "endometriosis" and "infertility" (1988-1990). From the resulting downloaded data base on endometriosis and infertility, publications were chosen for inclusion on the basis of their relevance to the specific subject of physiological links between endometriosis and infertility.

Approximately 20 periodical indexes were also searched for publications, via a data base being prepared for The Endometriosis Network of Toronto (TENT), but professional publications in these indexes did not discuss as their primary subject the physiological links between endometriosis and infertility.

The result of the search on MEDLINE and Excerpta Medica is approximately 14 reviews and 79 clinical studies, which are accordingly separated into the sections "Reviews" and "Clinical Studies."

The "Reviews" were included for their general references to clinical studies dating before, as well as after, 1985, the cut-off date of this annotated bibliography.

The same policy was followed for both bibliographic sections, "Reviews" and "Clinical Studies." Credit is given to MEDLINE or Excerpta Medica for annotations excerpted from their data bases by prefacing their annotations with "MEDLINE" or "Excerpta Medica." MEDLINE and Excerpta Medica annotations are themselves quotes from abstracts, introductions, or summaries in the original sources. Annotations with no prefatory credit were written by the researcher, after reviewing the original source article.

Many entries in the "Clinical Studies" section describe the outcomes of multiple tests. As a result, an article might cover material addressed in several subsections. Each article was assigned to what seemed its most appropriate subsection. But a reader interested in all possible articles on a given issue will need not only to read the relevant subsection, but to scan other subsections of the annotated bibliography for bold-typed reference to the issue. All terms within the annotations that are relevant to any of the annotated bibliography's subsections are printed in bold, to enable the reader to browse for a specific issue throughout the annotated bibliography. Similarly, in the "Reviews" section, relevant terms are highlighted to facilitate browsing.

Part of the original research design was to determine the ratio of findings for suggested links, no link, or direct links between endometriosis and infertility on the physiological and biochemical levels. Most of the studies conclude by suggesting that a link may exist between endometriosis and infertility; some show no link, and only a minority demonstrate a clear

link. Because articles discuss multiple issues, and because findings differ from issue to issue, it is not possible to state that x number of studies as a whole suggest a link, find no link, or assert a direct link. To generalize from all articles cited in the annotated bibliography, a link is suggested approximately 85 percent of the time, no link is indicated approximately 10 percent of the time, and a direct link is specified the remaining 5 percent of the time. Because the annotated bibliography does not reference all of the studies reported on the subject, the findings presented here are not necessarily indicative of the total body of research published. Notations are provided between the article headings and the annotations, to specify either a direct link or no link. This notation may relate to entire articles or to specific issues within articles. Where it relates to a specific issue, the term referred to in the annotation follows the notation after the title. Where there is no notation, a link can be assumed to be suggested by the researchers. To search the annotated bibliography for any studies that specify a definite link or no link, one need only scan the entries for the notation, then read the article referenced or the highlighted keyword.

The marker "no link" does not mean that the authors conclude that no link at all exists between endometriosis and infertility. "No link" means that the findings of a particular study were negative. The same holds true for "direct link," which means that the findings of a particular study were positive in the one issue examined, not that endometriosis and infertility are in all ways related.

The same marker system was used to indicate the entries in the "Reviews" section that posited "no link" between endometriosis and infertility.

Reviews

Entries/keywords suggest link unless otherwise indicated

Ory, S.J. 1987. "Pelvic Endometriosis." *Obstetrics and Gynecology Clinics of North America* 14: 999-1014. Professional Journal

"Presently, it is not clear why some individuals with endometriosis develop infertility and pelvic pain, whereas others with a similar degree of disease do not. Several tantalizing clues have been extracted from studies of the molecular pathogenesis, immunology, and biochemistry of endometriosis. Investigations are now under way to determine the specific relevance to infertility of macrophage aggregation; prostaglandin and related metabolite production by endometriotic lesions and macrophages; specific factors released by endometriosis that might directly impair ovum pick-up, fertilization, embryo transfer, or implantation; and ovulatory dysfunction including luteal phase deficiency and LUFS. There are probably a host of potential mechanisms of infertility in endometriosis; additional research should enable us to determine their regulatory features and to formulate effective clinical intervention.

"We now have a broader array of options for the treatment of endometriosis than ever before. However, most of the extant reported clinical experience consists of case reports and limited series of patients without the use of controls, follow-up intervals, and appropriate statistical analysis. The diverse course and presentation of the disease have limited our ability to develop a staging system that provides consistent scoring among different clinicians and appropriate relative emphasis on the various manifestations of the disease. Some additional resolution will be necessary to assess the relative contribution to infertility by fresh and recurrent lesions, endometriomas, and adhesions."

Gibbons, W.E. 1988. "Peritoneal Fluid Embryo Toxicity." Seminars in Reproductive Endocrinology 6: 269-72. Professional Journal

Gibbons elaborates on an earlier study by Morcos et al. (1985).

He summarizes: "In a mouse embryo system we reported that **peritoneal fluid** obtained from women with endometriosis demonstrated a higher incidence of embryo toxicity than from women without endometriosis." He now reports that "since toxicity is occasionally seen in infertile patients without endometriosis ... the toxic reaction may occur by other mechanisms than just endometriosis." The researcher notes that the **immune system** might be involved: studies have reported increased counts and concentrations of **macrophages** and **interleukin-1**, and reduced **motile sperm survival** in peritoneal fluid. But "it is not clear if the observed changes noted in the peritoneal fluid of endometriosis patients are a result of or precede the endometriosis implants."

Wheeler, J.M., and L.R. Malinak. 1988. "Does Mild Endometriosis Cause Infertility?" Seminars in Reproductive Endocrinology 6: 239-49. Professional Journal

"Future studies need to address ... causality issues in a scientifically sound research design, with properly constructed control groups. Only with rigorous clinical research will we finally determine if mild endometriosis really does cause infertility."

Pittaway, D.E. 1988. "Endometriosis and Spontaneous Abortions." Seminars in Reproductive Endocrinology 6: 257-62. Professional Journal

no link - spontaneous abortions

Pittaway points out that "in order to establish a causal role of endometriosis in **spontaneous abortions**, potential mechanisms by which endometriosis may adversely influence an early gestation should be considered ... Many factors that have been implicated as possible mechanisms of endometriosis in reducing fertility may also play a role in the early failure of an **implanted embryo**."

But he also cautions that "the proportion of **spontaneous abortions** that may be attributable to endometriosis is much smaller than originally concluded. Furthermore, the growing body of data from comparative studies and from analyses of pregnancy outcomes of women with untreated

endometriosis has not supported a causal role of endometriosis in **spontaneous abortion**."

Metzger, D.A., and A.F. Haney. 1988. "Endometriosis: Etiology and Pathophysiology of Infertility." *Clinical Obstetrics and Gynecology* 31: 801-12. Professional Journal

"In spite of the apparent association of infertility and endometriosis, there is a paucity of evidence to identify a clear cause-and-effect relationship or to clarify the specific mechanism(s) of infertility due to this enigmatic disease. Areas that warrant additional attention include the effect of endometriosis on **ovulation**, the impact of the **immune system** on the development of endometriosis, and the effect of **peritoneal inflammation** on reproduction. A better understanding of these areas will lead to more efficacious and specific therapies for endometriosis-associated infertility."

Bancroft, K., C.A. Vaughan Williams, and M. Elstein. 1989. "Minimal/Mild Endometriosis and Infertility. A Review." *British Journal of Obstetrics and Gynaecology* 96: 454-60. Professional Journal

The authors summarize clinical studies on endometriosis and infertility dating from 1971 to 1987. They focus on minimal/mild endometriosis, since "it is not difficult to appreciate that moderate or severe disease [Revised American Fertility Society Classification greater than 16] can prevent conception." The cause: "Significant distortions," such as "adhesions, fibrosis or significant ovarian disruption by endometriomata."

A study by Acosta et al. (1973) confirmed by Buttram (1979) concluded that even mild endometriosis causes infertility. But seven later studies (dating from 1977 to 1987) found no significant difference in the fertility of women treated or left untreated for minimal/mild endometriosis.

Researchers have found higher levels of **prostaglandins** (1981 to 1986 — conflicting results) and **macrophages** (1981 to 1986 — in agreement) in the peritoneal fluid of women with minimal/mild endometriosis. Such higher levels have been shown to (1) alter tubal motility, (2) cause ovarian dysfunction, (3) reduce sperm motility or survival, (4) alter sperm-egg interaction, and (5) cause failure of early embryo development — all contributing to infertility. "**Interleukin-1**, a protein produced by **macrophages**," and "**sperm phagocytosis**" in activated **macrophages** are greater in women with minimal/mild endometriosis, and might contribute to infertility.

Defective ovarian functions, such as **anovulation**, **luteal phase dysfunctions**, and possible (reports conflict) **luteinized unruptured follicle (LUF) syndrome** "may coexist with endometriosis," thereby contributing to infertility. The causal relationship "remains unclear."

Researchers have discovered **autoimmune phenomena** in women with minimal/mild endometriosis sufficient to "warrant further investigation."

Many of the above complications can co-exist; no one abnormality is necessarily the cause of infertility in women with minimal/mild endometriosis. "The multiplicity of these abnormalities suggests that the

development of endometriosis may be a common consequence of these, rather than their cause, and as such, treatment of the disease will not necessarily improve infertility."

Guzick, D.S. 1989. "Clinical Epidemiology of Endometriosis and Infertility." Obstetrics and Gynecology Clinics of North America 16: 43-59. Professional Journal

Within an article that reviews the prevalence of endometriosis, its characteristics, and the efficacy of treatment, the author includes a section on endometriosis and infertility. He posits an association between endometriosis and infertility based on "epidemiologic evidence": "Infertile women are seven to ten times more likely to have endometriosis than are their fertile counterparts, and women treated for endometriosis who ultimately conceive do so at one third the rate observed in normally fertile women." He reviews the mechanisms that might cause infertility in women with minimal/mild endometriosis ("menstrual cycle physiology, immunologic factors, and peritoneal fluid"). He concludes: "Taken together, these findings provide a compelling explanation for the association between endometriosis and infertility."

Mahmood, T.A., and A.A. Templeton. 1989. "Minimal/Mild Endometriosis and Infertility." *British Journal of Obstetrics and Gynaecology* 96: 1248-49. Professional Journal

The authors remark on Bancroft's and his colleagues' review article (1989). They contend that studies "do suggest a strong association, but this is not the same as the suggestion that endometriosis is causal." They describe their own study (1989) in which they added a possible complicating factor — subfertile male partners could result in female partners diagnosed as infertile. Their "findings provide some evidence that mild endometriosis may not be the primary cause of infertility in all the women [in their study], and that it is possible that infertility for other reasons may predispose to or exacerbate the tendency to develop endometriosis in susceptible women."

Bancroft and his colleagues respond. They reiterate that they posited no causal relationship between endometriosis and infertility, that the "causality of the association ... remains a matter for debate." They repeat their conclusion that endometriosis might be a consequence, not a cause, of the multiple abnormalities reviewed in their paper. They remark in closing that Mahmood's and Templeton's "own work added further evidence to support our conclusion."

Surrey, E.S., and J. Halme. 1989. "Endometriosis as a Cause of Infertility." *Obstetrics and Gynecology Clinics of North America* 16: 79-91. Professional Journal

"The link between advanced forms of endometriosis and infertility has been fairly well established. The association between mild or minimal stages of the disease and lessened fertility is much more tenuous. In the absence of information on the prevalence of endometriosis in the general population, epidemiologic conclusions can only remain speculative. On the basis of our understanding of the current body of literature, the cause of infertility in patients with endometriosis appears to be multifactorial. Chronic **inflammatory changes** secondary to activation of **local immune mechanisms** play a large role in creating an environment hostile to **ovum capture**, **fertilization**, and **transport** as well as **implantation**. Central and local factors may also impair normal **ovulatory and corpus luteum function**." Mechanisms reviewed include mechanical factors, changes in the **peritoneal fluid** environment, activation of **local or systemic immune response**, and abnormalities of **ovulation**, **fertilization**, and **early pregnancy**.

The reviewers note that "most of the current information is based on retrospective analysis." They express hope for "well-designed and controlled prospective clinical and basic investigations in the future."

Wheeler, J.M. 1989. "Epidemiology of Endometriosis-Associated Infertility." *Journal of Reproductive Medicine* 34: 41-46. Professional Journal

no link (entry)

"As a cause of infertility, especially in its milder forms, when anatomic distortion of the tube and ovary is slight, endometriosis simply has not been proven to be a cause of infertility." Because clinical studies examine "highly selected groups of women presenting with pelvic pain or infertility," bias is inherent in their findings. Statistics for prevalence in the general population are based on artificially defined subgroups, which do not adequately represent the whole population (for example, women diagnosed by the same surgical procedure). Selection bias must be eliminated from clinical studies in order to achieve more representative statistics.

"Few authors have attempted to prove that endometriosis actually causes infertility." Clinical studies of endometriosis and infertility fail to satisfy six of Sackett's nine tests for causation. "It is the seventh criterion, biologic plausibility, on which most 'causative' research has been performed to date; clearly, enough plausible mechanisms have been proposed for endometriosis-associated infertility to satisfy this relatively low ranked criterion." But as a whole, "the evidence is very weak at best." Wheeler advocates epidemiological research rather than biological research to ascertain the relationship.

Burns, W.N., and R.S. Schenken. 1989. "Pathophysiology." In Endometriosis: Contemporary Concepts in Clinical Management, ed. R.S. Schenken. Philadelphia: J.B. Lippincott. Professional Monograph

The authors review studies of mechanical factors in endometriosis and infertility: **anatomic distortion** and **tubal obstruction** ("accepted as an explanation for infertility"); **anovulation**, **luteal phase defects**, and **hormonal abnormalities** ("evidence ... is weak and contrary evidence is

substantial"); **galactorrhoea/hyperprolactinaemia** ("insufficient evidence"); **luteinized unruptured follicles** (not the predominant or sole cause, but might interact with other pathophysiologic mechanisms to "at times cause infertility"); **autoimmunity** ("intriguing," but needs "more convincing evidence using specific techniques"); **peritoneal macrophages** and the **peritoneal inflammatory response** ("evidence is not strong enough;" "further research ... is needed"); **peritoneal fluid prostaglandins** ("further studies in humans are needed"); and **spontaneous abortions** ("there is no substantial evidence").

Halme, J., and E.S. Surrey. 1990. "Endometriosis and Infertility: The Mechanisms Involved." *Progress in Clinical and Biological Research* 323: 157-78. Professional Journal

"An association between endometriosis and infertility is generally assumed, but most of the studies in support of this are based on retrospective analysis. The link appears stronger for advanced forms of endometriosis whereas the association between minimal or mild stages of the disease and lower fecundity is much more tenuous.

"We do not attempt to critically evaluate this basic premise but instead review some of the existing information regarding the myriad of mechanisms proposed to explain the association between endometriosis and infertility."

Mechanisms reviewed include: "anatomic factors," "ovulatory-hormonal dysfunction," "abnormal fertilization," "early pregnancy loss," "altered systemic immunity," "altered peritoneal fluid local immune response," and "evidence for reproductive toxicity in endometriosis."

Rönnberg, L. 1990. "Endometriosis and Infertility." *Annals of Medicine* 22: 91-96. Professional Journal

"The relationship of endometriosis, the most common benign gynaecological disease during reproductive life, to infertility is generally ill understood. The association between infertility and minimal to mild endometriosis, when no anatomical defect is evident, may be explained by the following possible mechanisms: alterations in peritoneal fluid (macrophages — immunoglobulins, Interleukin-1, protease inhibitors, prostanoids, an ovum capture inhibitor), ovulatory dysfunctions (anovulation, LUF syndrome), luteal phase defect, disturbed implantation, and spontaneous abortion. These possibilities are discussed. The latest prospective controlled studies offer strong evidence that endometriosis per se is not a direct cause of infertility. On the other hand, the disease usually deteriorates if not treated, and therefore medical or surgical interventions are often needed when expectant treatment or other infertility therapies, e.g., ovulation induction, fail to result in pregnancy. Women with minimal to mild endometriosis only should be diagnosed as having unexplained infertility, which today may be treated by in vitro fertilization."

Rock, J.A., and B.S. Hurst. 1990. "Clinical Significance of Prostanoid Concentration in Women with Endometriosis." *Progress in Clinical and Biological Research* 323: 61-80. Professional Journal

"Because of the potential for alterations in the reproductive system, an alteration of prostanoids has been proposed as a mechanism for endometriosis associated infertility." The researchers discuss the role prostaglandins play in reproduction, and review the relationship between prostaglandins and endometriosis. In reproductive systems, prostaglandins affect (1) ovulation: studies have addressed abnormal follicular development, luteinized unruptured follicle syndrome, oligoovulation, and luteal phase deficiency (findings are inconclusive); (2) tubal motility: studies have addressed 15-methyl-PGF2-alpha (findings conflict), and oocyte and embryo transport (findings are inconclusive); (3) luteolysis: studies have addressed luteal regression and premature luteolysis (findings are inconclusive), and luteal phase deficiency (findings are inconclusive); (4) uterine contractility/implantation: studies have addressed prostaglandins (findings are inconclusive), and spontaneous abortion (findings are contradictory); (5) embryogenesis: studies have addressed heat-inactivated peritoneal fluid (findings of one study are positive) and interleukin-1 (findings of one study are positive); (6) endometrial implants: one study has proposed that implants cause a peritoneal reaction leading to infertility; and (7) peritoneal fluid prostaglandin levels: (findings conflict). To account for contradictory findings, one study concluded that "prostaglandin production may be altered with the histology of the endometrial implants." The researchers conclude that this last study's findings "suggest that in vitro incubation techniques may be more useful than direct measurement of prostaglandin content" and that "this data also suggests that the current classification system may be insufficient with regards to activity of the disease."

Clinical Studies

Reproductive Cycle Factors

Tummon, I.S., et al. 1988. "Occult Ovulatory Dysfunction in Women with Minimal Endometriosis or Unexplained Infertility." Fertility and Sterility 50: 716-20. Professional Journal

Excerpta Medica: Characteristics of **follicular development** and **hormonal patterns** were evaluated in 17 women with minimal endometriosis and 11 with unexplained infertility. The controls were 7 women with male factor infertility and 8 who conceived during an investigational cycle. Women with minimal endometriosis had more and smaller **follicles** at **luteinizing hormone (LH)** surge, lower preovulatory **estradiol** (E_2), and lower E_2 at LH surge ... Occult **ovulatory dysfunction** may contribute to infertility in women with minimal endometriosis or unexplained infertility.

Fedele, L., et al. 1990. "Structural and Ultrastructural Defects in Preovulatory Endometrium of Normo-Ovulating Infertile Women with Minimal or Mild Endometriosis." Fertility and Sterility 53: 989-93. Professional Journal

MEDLINE: To investigate whether a primary endometrial factor is involved in the pathogenesis of infertility in patients with minimal or mild endometriosis, we compared light, scanning, and transmission electron microscopic studies of preovulatory endometria of 15 endometriotic patients with 12 normal controls. All the women were infertile and normo-ovulating by standard criteria. Six morphometric indexes were considered. The scanning electron microscopic analysis revealed heterogeneity of the endometrial surface epithelium in 77% of the patients with endometriosis and in 16% of the controls. Glandular and stromal mitoses, basal vacuolated cells, and the ciliated:nonciliated cell ratio was significantly reduced in the endometriosis group compared with the controls. Further studies are needed to clarify the role of the observed endometrial anomalies in the pathogenesis of infertility associated with endometriosis.

Chew, P.C., et al. 1990. "Elevated Peritoneal Fluid Luteinizing Hormone and Prolactin Concentrations in Infertile Women with Endometriosis." International Journal of Gynecology and Obstetrics 33: 35-39. Professional Journal

MEDLINE: In this study, we compared (Mann-Whitney U-test) the peritoneal fluid FSH, LH and PRL levels, measured by RIA, at the follicular and luteal phases of the menstrual cycle in [43] women [aged 25-44] with [endometriosis] and [35 women, aged 25-39] with no evidence of endometriosis who were considered as controls ... The results suggest that disordered synchronization of **neuroendocrine mechanisms** controlling **LH and PRL** may be the underlying abnormality causing infertility in our group of patients with endometriosis.

SEE ALSO "Reviews" and subsections that here follow for further mention of reproductive cycle issues.

Follicular Phase Defects

Thomas, E.J., E.A. Lenton, and I.D. Cooke. 1986. "Follicle Growth Patterns and Endocrinological Abnormalities in Infertile Women with Minor Degrees of Endometriosis." *British Journal of Obstetrics and Gynaecology* 93: 852-58. Professional Journal

no link (entry)

"Eighteen patients whose only demonstrable cause of infertility was a minor degree of endometriosis and whose partners were normal, were investigated prospectively for one menstrual cycle using ultrasonography and endocrine profiles. Twelve cycles appeared to be normal. A **luteinized unruptured follicle (LUF)** occurred in two cycles and one patient had a follicular cyst. In a further two patients there was **inadequate or abnormal folliculogenesis** whilst in the last patient the **follicle ruptured**

prematurely. This study describes the variety of endocrinological abnormalities found in women with mild endometriosis, and concludes that, in this series at least, there is a low frequency of **LUF**."

SEE ALSO "Reviews" and other "Reproductive Cycle Factors" subsections for further mention of follicular phase defects.

Ovulatory Phase Defects

Shrivastav, P., et al. 1988. "Follicular Fluid Histamine Concentrations in Infertile Women with Pelvic Adhesions." *Acta Obstetricia et Gynecologica Scandinavica* 67: 727-29. Professional Journal

"Dense pelvic adhesions can arise as a result of pelvic infection, endometriosis, peritonitis, or pelvic surgery. The burnt-out disease is associated with evidence of a chronic inflammatory response. One of the chemical mediators of inflammation is histamine; and human and animal studies have indicated a role for histamine in the ovulatory process. In [8] women with dense pelvic adhesions [as a result of chronic pelvic inflammatory disease, endometriosis, or previous tubal surgery] we have found significantly elevated concentrations of **histamine in the follicular fluid** when compared with the follicular fluid obtained from [12] women without adhesions. This may lead to **premature ovulation** during a normal cycle, resulting in the release of an immature oocyte. It is possible that this may contribute to the lower fertility in women who have pelvic endometriosis but patent fallopian tubes, and in those patients where tubal patency has been restored following tubal surgery."

Kaplan, C.R., et al. 1989. "Effect of Ovarian Endometriosis on Ovulation in Rabbits." *American Journal of Obstetrics and Gynecology* 160: 40-44. Professional Journal

Excerpta Medica: To study the relationship between endometriosis and ovulatory dysfunction, we induced ovarian endometriosis in the rabbit model. Adipose tissue was placed in the contralateral ovary as a control. Ovulation was induced with human chorionic gonadotropin and ovulation points were counted before and after induction of endometriosis. Periovarian adhesions were graded, and ovaries were histologically examined. A significant decrease in the number of ovulation points was observed in ovaries with endometrial tissue (p = 0.001) but not in ovaries that contained adipose tissue (p = 0.095). Periovarian adhesions decreased the number of ovulation points (p less than 0.01) in ovaries that contained adipose or endometrial tissues. Multivariate analysis demonstrated that an increase in adhesion severity was correlated with a decrease in the number of ovulation points (p less than 0.05), but endometrial tissue was not (p = 0.45). We conclude that, in the rabbit model, minimal ovarian endometriosis impairs ovulation primarily through a mechanism related to periovarian adhesions.

SEE ALSO "Reviews" and other "Reproductive Cycle Factors" subsections for further mention of ovulatory phase defects.

Anovulation

Arumugam, K., T.A. Mahmood, and Y.F. Kong. 1989. "The Association of Anovulation and Endometriosis in the Infertile Female." *Australian and New Zealand Journal of Obstetrics and Gynaecology* 29: 350-51. Professional Journal

direct link (entry)

MEDLINE: Ninety-six infertile patients with endometriosis were studied and their endometriosis staged according to the Revised American Fertility Society Classification. **Anovulation** was detected in 19% of the 32 patients with Stage I disease but in only 3% in the remaining 64 patients with Stage II, III and IV disease. These results show that contrary to traditional belief, **anovulation** does occur in a significant number of patients with endometriosis, especially in minimal or mild disease.

SEE ALSO "Reviews" and other "Reproductive Cycle Factors" subsections for further mention of anovulation.

Luteinized Unruptured Follicle (LUF) Syndrome

Holtz, G., et al. 1985. "Luteinized Unruptured Follicle Syndrome in Mild Endometriosis. Assessment with Biochemical Parameters." *Journal of Reproductive Medicine* 30: 643-45. Professional Journal

MEDLINE: Failure to extrude an ovum, with subsequent luteinization of the unruptured follicle (LUF), has been proposed as a cause of infertility in women with mild endometriosis. To assess the incidence of this process we performed laparoscopies in the early luteal phase on 16 women with mild endometriosis and 8 control subjects ... Findings suggest that LUF occurs occasionally in association with mild endometriosis. Additionally, ovarian steroidogenesis, particularly P secretion, was impaired frequently in the absence of LUF in women with endometriosis.

Donnez, J., et al. 1987. "Syndrome du follicle lutéinisé non rompu et endométriose expérimentale chez la lapine." *Journal de Gynécologie obstétrique et Biologie de la Reproduction* 16: 871-76. Professional Journal

MEDLINE: To study the effect of endometriosis on follicular rupture, endometrial tissue was autografted to New Zealand White rabbits. Endometrium was surgically implanted into the peritoneal cavity. Human chorionic gonadotropin was administered to induce ovulation. The viability of the implants was demonstrated histologically during three subsequent laparotomies ... Our data demonstrated that endometriosis induced a failure of follicular rupture.

SEE ALSO "Reviews" and other "Reproductive Cycle Factors" subsections for further mention of luteinized unruptured follicle (LUF) syndrome.

Abnormal or High Prolactin Secretion

No complete articles are available for this subject. SEE "Reviews" and other subsections of "Peritoneal Fluid Factors" for mention of galactorrhoea and hyperprolactinaemia in other studies.

Ovum Capture Inhibitor (OCI)

Suginami, H., et al. 1986. "A Factor Inhibiting Ovum Capture by the Oviductal Fimbriae Present in Endometriosis Peritoneal Fluid." Fertility and Sterility 46: 1140-46. Professional Journal

direct link (entry)

This study was conducted "with a working hypothesis that there might be a substance inhibiting the cumulus-fimbria interaction in endometriosis PF [peritoneal fluid], which might cause the failure in ovum capture by the oviductal fimbria, resulting in infertility." The researchers incubated oviductal fimbriae from adult female Golden hamsters with "native and pretreated PF aspirated from patients with [15] and without [9] endometriosis." "Although the two groups of patients who participated in the study were not fully matched, the data obtained were quite conclusive." "A factor inhibiting fimbrial capability of **ovum capture** is present in endometriosis PF [**peritoneal fluid**]."

Luteal Phase Defects (LPD)

Tzingounis, V., and P. Maghioracos. 1985. "Insuffisance lutéale et endométriose. Étude comparative de la progesterone plasmatique et du stade évolutif." *Journal de Gynécologie obstétrique et Biologie de la Reproduction* 14: 455-58. Professional Journal

no link (entry)

MEDLINE: 24 patients who had more than two years of infertility were checked by laparoscopic and hormone (**plasma progesterone**) tests at the 21st-23rd day of the cycle. Two comparable groups were found: Group A with no visible endometriosis, and Group B with obvious endometriosis (stage I, IIa, IIb according to Kistner's classification). There is a significant difference between the two groups as far as the levels of **progesterone** in the plasma are concerned, because they are lower in Group B than in Group A. On the other hand, there is no correlation to be demonstrated between the severity of the endometriosis and the low level of **progesterone**.

Balasch, J., and J.A. Vanrell. 1985. "Mild Endometriosis and Luteal Function." *International Journal of Fertility* 30 (3): 4-6. Professional Journal

no link (entry)

MEDLINE: The luteal function of 27 patients with mild endometriosis and infertility was compared with that of 50 infertile patients without endometriosis. The incidence of endometrial **luteal phase deficiency** was similar in both groups of patients. Luteal phase length and plasma levels

of **progesterone** (P), **estradiol** (E_2) and **prolactin** (PRL) in infertile patients (both groups) were similar to those in a group of 10 fertile women. We conclude that **luteal phase defects** should not be considered as a primary cause of infertility in mild endometriosis.

Balasch, J., et al. 1986. "Early Luteal Function Following Danazol Therapy for Endometriosis." *Human Reproduction* 1: 291-93. Professional Journal

no link (entry)

MEDLINE: The **luteal phase** of 20 infertile women with endometriosis who were treated with danazol (600 mg daily for 6 months) was studied by **basal body temperature**, **plasma progesterone** (P), **oestradiol** (E_2) and **prolactin** (PRL) determination, and endometrial biopsy, in any one of the first three cycles after discontinuation of danazol. All endometrial specimens were noted to be fundal samples and were clearly progestational after danazol therapy. **Abnormal secretory phases** were detected in three patients, as in the pre-danazol control cycles. Moreover, plasma levels of P, E_2 and PRL in post-danazol cycles were similar to those found in control cycles and fell within the normal range in all cases except for one patient having **hyperprolactinaemia**. In conclusion, our study shows that endometrial inadequacy is not the cause of the increased fetal wastage previously reported among proximally conceived pregnancies after danazol therapy for endometriosis.

Williams, C.A., M.K. Oak, and M. Elstein. 1986. "Cyclical Gonadotrophin and Progesterone Secretion in Women with Minimal Endometriosis." Clinical Reproduction and Fertility 4: 259-68. Professional Journal

MEDLINE: Concentrations of **LH**, **FSH**, **oestradiol** (**E**) and **progesterone** (**P**) were measured in serum of 12 women with minimal endometriosis and otherwise unexplained infertility. Values were compared with those on corresponding days relative to the pre-ovulatory LH peak (Day 0) in six fertile women. Three women exhibited cycle profiles of LH, FSH, E and P indistinguishable from those in the control group. In the remaining nine women cycle profiles for FSH and follicular phase profiles for LH were normal but eight exhibited a delay in P secretion and reduced total P output. LH concentrations were elevated during the early luteal phase in five subjects, two of whom had a second LH surge. These data suggest that **luteal dysfunction** and **abnormal secretory patterns for LH** may be contributory to infertility associated with endometriosis.

Ayers, J.W., D.L. Birenbaum, and K.M. Menon. 1987. "Luteal Phase Dysfunction in Endometriosis: Elevated Progesterone Levels in Peripheral and Ovarian Veins During the Follicular Phase." Fertility and Sterility 47: 925-29. Professional Journal

MEDLINE: Endometriosis has been associated with corpus luteum inadequacy and abnormalities of luteal phase progesterone (P) secretion. In this study, abnormal luteolysis, as a second factor of luteal

dysfunction, was assessed in 13 women with endometriosis and 25 control patients by measurement of ovarian vein estradiol (E_2) and P during the follicular phase. The results reveal that women with endometriosis have (1) significantly lower ovarian vein E_2 [**estradiol**], (2) significantly higher both peripheral and ovarian vein P [**progesterone**], and (3) threefold higher P/ E_2 ratios than controls during the **follicular phase**. These data support the concept of continued P production from an active **corpus luteum** well into the **follicular phase** of the following cycle in women with endometriosis. Failure of adequate **luteolysis** is a second aspect of **luteal dysfunction** in endometriosis and strongly supports the growing body of data confirming **ovulatory asynchrony** in the minimal endometriosis infertility syndrome.

Radwanska, E., I. Henig, and W.P. Dmowski. 1987. "Nocturnal Prolactin Levels in Infertile Women with Endometriosis." *Journal of Reproductive Medicine* 32: 605-608. Professional Journal

MEDLINE: Both hyperprolactinemia and endometriosis are associated with infertility. A study was performed to ascertain whether **sleep-related prolactin (PRL) hypersecretion** was present in endometriosis. Fifty-five consecutive infertile women with regular menstrual cycles and admitted for diagnostic laparoscopy were studied. Blood samples were drawn throughout the night preceding surgery. Serum PRL, estradiol and progesterone levels were measured with radioimmunoassays. Nocturnal patterns of PRL secretion may be altered in infertile women with endometriosis, with an exaggerated and prolonged nocturnal peak. This alteration in PRL dynamics may contribute to infertility in women with endometriosis and may be a part of the pathophysiology of this disease.

Ji, H. 1989. ["Luteal Function in Patients with Endometriosis."] Chung Kuo I Hsueh Ko Hsueh Yuan Hsueh Pao 11: 344-48. Language: Chinese. Professional Journal

MEDLINE: Luteal function was studied in 19 cases with endometriosis, infertility being present in 16 cases ... In conclusion, the incidence of **luteal phase defect (LPD)** is higher in [the] endometriosis group than that in the controls. The mechanisms of LPD and its relationship with infertility were discussed.

Hayashi, N., Y. Taketani, and M. Mizuno. 1989. ["Relationship Between Luteal Function and Prolactin in Infertile Women with Endometriosis."] Nippon Sanka Fujinka Gakkai Zasshi 41: 1720-24. Language: Japanese. Professional Journal

no link - prolactin

MEDLINE: Luteal function in 44 infertile women with endometriosis [was] studied with reference to **prolactin (PRL)** and compared with 34 unexplained infertile women without endometriosis ... Results indicate the close association of endometriosis with an inadequate **luteal phase**. However, it seems that the aberrant secretion of **PRL** has no relation to the **impaired luteal function** in endometriosis.

Zhang, Y.W., et al. 1989. "Luteal Function in Patients with Endometriosis." Proceedings of the Chinese Academy of Medical Sciences and the Peking Union Medical College 4 (2): 96-101. Professional Journal

MEDLINE: Nineteen patients with endometriosis were selected for investigation of luteal function as determined by serum progesterone (P) concentrations at different stages of the luteal phase, and by observation of basal body temperature (BBT) profiles and endometrial histological appearances. Sixteen cases were accompanied with infertility ... In summary, the incidence of **luteal phase defect** was higher in the endometriosis group than in controls. The pathogenic mechanism of **luteal phase defect** and its role in infertility are discussed.

SEE ALSO "Reviews" and other "Reproductive Cycle Factors" subsections for further mention of luteal phase defects.

Peritoneal Fluid Factors

Direct Toxicity of Peritoneal Fluid

Sperm Function

Dorez, F., et al. 1985. "Immobilisation des spermatozoïdes par le liquide péritonéal de femmes stériles. Premiers résultats." Journal de Gynécologie obstétrique et Biologie de la Reproduction 14: 295-99. Professional Journal

MEDLINE: **Peritoneal fluid** from sterile women where the state of the pelvis is changed by endometriosis, inflammation, infection, and in certain cases where it appears normal laparoscopically, can immobilise **spermatozoa** in minutes or hours. This **toxicity** against male gametes could be an explanation of the mechanism for such sterility. The tubes and the ovaries are bathed in this liquid in the periovulatory phase when they are largest in size. If these first observations are confirmed fully many theoretical, practical and therapeutic implications must follow.

Dorez, F., F. Cavaillé, and C. Sureau. 1985. "Hypothèses relatives aux variations de mobilité des spermatozoïdes dans le liquide péritonéal." Journal de Gynécologie obstétrique et Biologie de la Reproduction 14: 955-58. Professional Journal

MEDLINE: We have studied the effects on **sperm motility** in **peritoneal fluid** taken from fertile women at different times of the cycle as well as from sterile women in the pre-ovulatory phase. We have compared the effects on the movement of sperms in part in a solution of pure Tyrode and in part in a solution of Tyrode containing hydroxytoluene, which is an antioxydising agent, in order to try to find out the mechanism that immobilises sperms in these sterile women ... The female genital tract does undergo changes during the menstrual cycle which allow sperms to stay motile and that this is probably the same effect as the albumin mercaptoethanol complex. This equilibrium is broken when there are lesions in the pelvis such as endometriosis or inflammatory disease by secretion of

peroxydising substances such as fatty acids and the oligopeptides that occur in inflammation.

Oak, M.K., et al. 1985. "Sperm Survival Studies in Peritoneal Fluid from Infertile Women with Endometriosis and Unexplained Infertility." Clinical Reproduction and Fertility 3: 297-303. Professional Journal

"Peritoneal fluid (PF) volume and sperm survival (motility and velocity) were studied in PF from [20] women with unexplained infertility, [20] infertile women with endometriosis and [20] fertile women without endometriosis using a laser light scattering technique. PF volume was significantly larger in the group of women with unexplained infertility (P less than 0.025) and in infertile women with endometriosis (P less than 0.003) when compared with fertile women. There was a significant reduction in the percentage of motile sperm in women with unexplained infertility (P less than 0.001) and in infertile women with endometriosis when compared with fertile women (P less than 0.001). In infertile women with endometriosis a positive correlation was observed between peritoneal fluid volume and reduction in the percentage of motile sperms (P less than 0.01).

"It would appear from this small study that inhibition of **sperm motility and velocity** in PF may be a factor in the aetiology of infertility in women with endometriosis or otherwise unexplained infertility."

Stone, S.C., and K. Himsl. 1986. "Peritoneal Recovery of Motile and Nonmotile Sperm in the Presence of Endometriosis." *Fertility and Sterility* 46: 338-39. Professional Journal

no link (entry)

"It has been postulated that pelvic endometriosis may cause infertility by interfering with **sperm motility and transport** and even by increased intraperitoneal **phagocytosis**. [In a total of 106 patients,] the rate of sperm recovery at the time of laparoscopy performed in the immediate pre-ovulatory period was determined in 29 patients (27.4%) with endometriosis (AFS stage I) and in 77 patients (72.6%) without endometriosis. The number of patients with **motile sperm** in both groups was similar ... It is concluded that mild endometriosis does not affect **sperm transport and survival** and that increased **sperm phagocytosis** in vivo is unlikely."

Burke, R.K. 1987. "Effect of Peritoneal Washings from Women with Endometriosis on Sperm Velocity." *Journal of Reproductive Medicine* 32: 743-46. Professional Journal

MEDLINE: In a prospective study the author measured the "before" and "after" effects of in vitro washing and capacitation on **sperm characteristics** in 25 normospermic men using a microcomputerized system for semen analysis. Each fresh semen sample was divided into aliquots and assigned to one of four groups ... Group 4 [represented] sperm capacitated with HHS to which had been added 10% **peritoneal washings** in D5RL obtained from women with endometriosis (American Fertility

Society stages I and II) diagnosed at the time of diagnostic laparoscopy \dots The addition of peritoneal washings from women with proven endometriosis to the capacitation medium \dots had a marked and statistically significant (P less than 0.0001) detrimental effect. These results suggest that the adverse effect of endometriosis on fertility may be biochemically mediated.

Sueldo, C.E., et al. 1987. "The Effect of Peritoneal Fluid from Patients with Endometriosis on Murine Sperm-Oocyte Interaction." *Fertility and Sterility* 48: 697-99. Professional Journal

Researchers studied the cul-de-sac peritoneal fluid of 37 women at laparoscopy. Sixteen diagnosed with stages I and II of endometriosis at time of the operation were used as the endometriosis group and 21 fertile women who underwent surgery for sterilization were used as controls. By creating a mouse model of **sperm-oocyte interaction** using the aspirated peritoneal fluid, researchers determined that **peritoneal fluid** "contains some factor or factors that interfere with effective **gamete interaction**" and that peritoneal fluid "from patients with mild endometriosis has an increased activity of this substance and/or additional inhibitory factors." "In endometriosis," they continue, "this **peritoneal fluid factor or factors** appear to be filterable and to a significant degree heat-labile. This observation may be of importance in explaining subfertility associated with early stages of endometriosis."

Tan, G.J.S., et al. 1988. "Lack of Effect of Peritoneal Fluid from Endometriosis Patients on *In Vitro* Spermatic Function." *Medical Science Research* 16: 1263. Professional Journal

no link (entry)

Excerpta Medica: The effect of **peritoneal fluid** from mild endometriosis patients on in vitro **spermatic function** was studied.

Peritoneal fluid from endometriosis patients was found not to affect either **sperm motility** or their responses to a hypo-osmotic solution, suggesting that the antifertility effect of mild endometriosis is not due to its major action on spermatic function.

Inoue, M. 1989. ["Treatment of Endometriosis Associated Infertility."] Nippon Sanka Fujinka Gakkai Zasshi 41: 960-70; discussion 1000-1007. Language: Japanese. Professional Journal

no link (entry)

MEDLINE: During the last 13 years, 2 080 infertile patients were subjected to diagnostic laparoscopy. The mean age was 32.3 and their mean infertility period was 6.0 years. Of these, 1 263 (60.7%) patients were diagnosed to have endometriosis: 587 (46.5%) were stage I (R-AFS), 348 (27.6%) were stage II, 184 (14.6%) were stage III and 144 (11.4%) were stage IV ... To elucidate the mechanism of endometriosis associated infertility, peritoneal fluid volume, intratubal sperm transport (peritoneal sperm recovery test), and phagocytosis of sperm in the tube and in the peritoneal fluid were examined in more than 1 000 cases. However, no positive relationship was found between the disease and these parameters.

Fimbrial microbiopsy also revealed that endometriosis did not affect the ciliation index of the fimbria, nor changed the fine surface structure.

SEE ALSO "Reviews" and other subsections of "Peritoneal Fluid Factors" for further mention of the effects of peritoneal fluid on sperm.

Embryo Implantation and Development

Morcos, R.N., W.E. Gibbons, and W.E. Findley. 1985. "Effect of Peritoneal Fluid on *In Vitro* Cleavage of 2-Cell Mouse Embryos: Possible Role in Infertility Associated with Endometriosis." *Fertility and Sterility* 44: 678-83. Professional Journal

"The purpose of this study was to evaluate the effect of PF [peritoneal fluid] from [18] patients with endometriosis (PF-E) and from [10] patients with no evidence of endometriosis (PF-NE) on in vitro cleavage of 2-cell mouse embryos." Peritoneal fluid obtained from women with endometriosis demonstrated a higher incidence of **embryo toxicity** than from women without endometriosis. "This effect could be important in the mechanism of infertility in endometriosis without obvious pelvic adhesions."

Hahn, D.W., et al. 1986. "Experimental Evidence for Failure to Implant as a Mechanism of Infertility Associated with Endometriosis." *American Journal of Obstetrics and Gynecology* 155: 1109-13. Professional Journal

MEDLINE: The effect of endometriosis on pregnancy, from ovulation through day 14 of pregnancy, was studied in an animal model previously developed and validated with the use of the rabbit. Endometrial tissue was implanted surgically in rabbits and allowed to grow for 11 weeks without hormonal supplementation. The animals were artificially inseminated with semen from bucks with established fertility and human chorionic gonadotropin was administered to induce ovulation. The animals were put to death 1, 4, 8, or 14 days later. The number of corpora lutea and fertilized ova was not affected through day 4. However, on days 8 and 14, a significant reduction in the number of normal fetuses was observed. In a second experiment peritoneal fluid from animals with endometriosis was transferred to normal rabbits 1 day before artificial insemination. A significant reduction in the number of normal fetuses was observed. These studies suggest that failure of nidation due to the maternal environment may be a major factor in infertility associated with endometriosis.

Formelli, G., et al. 1990. "Effetti dell' endometriosi ovarica e peritoneale sulla fertilità. Studio sperimentale." ["Effects of Ovarian and Peritoneal Endometriosis on Fertility. Experimental Study."] Bolletino–Società Italiana Biologia Sperimentale 66: 129-34. Language: Italian. Professional Journal

MEDLINE: Fertility after ovarian and peritoneal endometriosis experimentally induced has been studied. The fertility rate in the animals with ovarian endometriosis was decreased [by] 40% and the same reduction was found in the animals with peritoneal endometriosis. Not only the direct

effect from adhesion formation, but also changes in the **peritoneal fluid or its constituents** are proposed as causes of endometriosis-associated infertility.

SEE ALSO "Reviews" for further mention of the effect of peritoneal fluid on embryo implantation and development.

Spontaneous Abortion

Metzger, D.A., et al. 1986. "Association of Endometriosis and Spontaneous Abortion: Effect of Control Group Selection." *Fertility and Sterility* 45: 18-22. Professional Journal

no link (entry)

MEDLINE: Endometriosis has been associated with an increased incidence of **spontaneous abortion**, compared with the abortion rate of the general population. To assess whether a separate control group would affect these conclusions, we studied 139 consecutive infertility patients with laparoscopically proven endometriosis to determine the incidence of **spontaneous abortion**. Ninety-five of these patients underwent conservative surgical resection of endometriosis, and 44 patients opted for expectant management. There was no significant difference between these two groups in average age, duration of fertility, or proportion of patients with primary infertility ... These results suggest that the **spontaneous abortion** rate in untreated endometriosis may not be as high as previously reported and may not be significantly different from the rate in the general population. The data also emphasize the need for well-defined control groups when assessing the effects of a treatment regimen.

FitzSimmons, J., et al. 1987. "Spontaneous Abortion and Endometriosis." Fertility and Sterility 47: 696-98. Professional Journal

no link (entry)

FitzSimmons and his colleagues report on a retrospective study of all patients with secondary infertility who underwent laparoscopy between 1 January 1977 and 31 December 1985 at the University of Wisconsin Clinical Sciences Center. Their results: "There was a slight excess of spontaneous abortions in the endometriosis group. However, this did not reach statistical significance, even by a two-sample test."

The researchers caution that in previous studies "selection bias for women with a history of a **spontaneous abortion**, coupled with a preponderance of women with a single loss or a previous successful pregnancy, could [have] contribute[d] to an apparently high rate of spontaneous loss before evaluation and the appearance of improvement after treatment."

Pittaway, D.E., C.P. Ellington, and M. Klimek. 1988. "Preclinical Abortions and Endometriosis." *Fertility and Sterility* 49: 221-23. Professional Journal

no link (entry)

MEDLINE: A single human chorionic gonadotropin determination was performed in 786 infertile women during the late luteal phase to determine the frequencies of **preclinical abortions** and whether the frequency was increased in women with endometriosis. Thirty-seven pregnancies (4.7% of cycles) were identified, of which six were classified as **preclinical abortions** (0.8%). In women with endometriosis, the frequency of **preclinical abortions** was 0.9% and was not statistically different from other infertile subgroups. This study suggests that **preclinical abortions** are not cause of infertility in either an infertile population as a whole or in the subgroup of women with endometriosis.

Pittaway, D.E., C. Vernon, and J.A. Fayez. 1988. "Spontaneous Abortions in Women with Endometriosis." *Fertility and Sterility* 50: 711-15. Professional Journal

no link (entry)

MEDLINE: Pregnancy outcomes were evaluated retrospectively in 350 women to investigate the relationship between endometriosis and **spontaneous abortions**. The frequency of **spontaneous abortions** in women with endometriosis was significantly higher than in both a fertile nonendometriosis group and an infertile group with tubal disease. There was no correlation beween the severity of the endometriosis and the frequency of **spontaneous abortions**. After treatment, the frequency of **spontaneous abortions** was significantly decreased in both the endometriosis and the tubal disease group, but these values were not significantly different from each other. We conclude that high **spontaneous abortion** rates are a characteristic of other subgroups of women with secondary infertility and not just in women with endometriosis, and that the majority of **spontaneous abortions** associated with endometriosis are not caused by the condition.

Olive, D.L. 1989. "Spontaneous Abortions in Women with Endometriosis." Letter. Fertility and Sterility 51: 1067. With reference to Olive, D.L. 1986. "Analysis of Clinical Fertility Trials: A Methodologic Review." Fertility and Sterility 45: 157-71. Professional Journal

no link (entry)

Olive points out that in his review he and his colleagues "concluded that endometriosis may not be the causative factor in the apparent high rate of prediagnosis **spontaneous abortions**." He adds: "We applaud Pittaway et al. for taking this one step further, and wholeheartedly endorse his conclusions."

SEE ALSO "Reviews" for further mention of spontaneous abortion.

Peritoneal Fluid Volume

Syrop, C.H., and J. Halme. 1986. "A Comparison of Peritoneal Fluid Parameters of Infertile Patients and the Subsequent Occurrence of Pregnancy." Fertility and Sterility 46: 631-35. Professional Journal "The effects of peritoneal fluid or its cellular components on human oocyte fertilization and cleavage cannot be studied directly. This report explores the association of laparoscopically obtained **peritoneal fluid volume**, **macrophage count**, **and concentration** of 124 infertility patients and their first occurrence of pregnancy during a 2-year follow-up period. Endometriosis patients who achieved pregnancy had a significantly lower mean **[peritoneal] fluid volume** than those remaining nonpregnant. In patients with endometriosis, a **fluid volume** significantly less than the mean for all endometriosis patients carries a significantly greater chance of pregnancy. The time required for the occurrence of pregnancy in patients with endometriosis appears influenced by **peritoneal fluid volume**. Peritoneal fluid of patients with endometriosis, via an as-yet-unknown mechanism or substance, appears to be associated with reduced fertility."

Marotta, L., and S.Z. Badawy. 1987. "Peritoneal Fluid and Pregnancy Occurrence." *Fertility and Sterility* 48: 700-702. Professional Journal no link — fluid volume

The authors comment on C.H. Syrop and J. Halme's article, "A Comparison of Peritoneal Fluid Parameters of Infertile Patients and the Subsequent Occurrence of Pregnancy" (1986). They reinterpret Syrop's and Halme's statistics by using the "Yates continuity correction factor" and an equation that allows "multivariate analysis" of the "interdependent variables." They suggest that biochemical and cellular changes, such as increases in **prostaglandins F_{2\alpha}, estradiol**, **acid phosphatase**, and **macrophages**, are changes "more significant than the **fluid volume**" in contributing toward infertility in patients with endometriosis.

SEE ALSO "Reviews" and other subsections of "Peritoneal Fluid Factors" for further mention of peritoneal fluid volume.

Prostaglandins

Badawy, S.Z., L. Marshall, and V. Cuenca. 1985. "Peritoneal Fluid Prostaglandins in Various Stages of the Menstrual Cycle: Role in Infertile Patients with Endometriosis." *International Journal of Fertility* 30 (2): 48-52. Professional Journal

MEDLINE: Thirty-nine patients with pelvic endometriosis and 45 patients with no evidence of endometriosis were entered in this study. The mean age was 29 years for each group. The **volume of peritoneal fluid** showed an increase towards the end of the cycle in both groups. Although the **volume** was higher in the endometriosis group than the control group, the difference between them was not significant. The concentration of **prostaglandins F_{2\alpha} and F_{2\alpha} was higher in patients with endometriosis than in the control group. The difference was significant (P less than 0.05) during days 9-16 and 17-24 for both prostaglandins**, and during days 1-8 for **prostaglandin F_{2\alpha}** only. The high concentration of **prostaglandins** in the periovulatory and early luteal phases of the cycle may have adverse effects on tubo-ovarian function in endometriosis patients. **Prostaglandin**

studies in peritoneal fluid are of significance during days 9-24 of the cycle when the effect of regurgitated menstrual fluid in the early phase of days 1-8 may be avoided.

Mudge, T.J., et al. 1985. "Peritoneal Fluid 6-Keto Prostaglandin $F_{1\alpha}$ Levels in Women with Endometriosis." *American Journal of Obstetrics and Gynecology* 152: 901-904. Professional Journal

no link (entry)

"Peritoneal fluid was collected from [42 women with endometriosis and 71 controls] undergoing investigations for infertility at laparoscopy performed during the luteal phase. The **volume of fluid** was recorded and concentrations of **6-keto prostaglandin \mathbf{F}_{1\alpha}** were determined by radio-immunoassay. No difference was found in either the total amount or the concentration of **6-keto prostaglandin \mathbf{F}_{1\alpha}** in the women with or without endometriosis. Furthermore, there was no difference in the **volume of peritoneal fluid** between these two groups of women. We conclude that **6-keto prostaglandin \mathbf{F}_{1\alpha}** in peritoneal fluid is not associated with macroscopically visible endometriosis."

Alber, D., et al. 1986. "Prostanoïdes du liquide péritonéal et stérilités associées ou non à des lésions pelviennes (endométrioses, adhérences post-infectieuses)." *Pathologie/Biologie* 34: 101-107. Professional Journal

MEDLINE: Peritoneal fluid levels of **6-keto-PGF**_{1 α}, **TxB**₂, **PGE**₂ and **PGF**_{2 α} were measured in 62 infertile women undergoing coelioscopy. In 10 patients with mild endometriosis, the levels of all **prostanoids** were significantly enhanced as compared to control group (15 infertile patients without pelvic [lesions]). In 5 patients with moderate endometriosis, only PGF_{2 α} exhibited a significant enhancement. The results confirmed the **prostanoid** component alteration of peritoneal fluid in infertile women with mild or moderate endometriosis, which however [has not] been found by all authors. The results of this study suggest that **prostanoids** are implicated in [the] physiopathology of endometriosis and pelvic adhesions and perhaps in [the] mechanism of ... associated infertility.

De Leon, F.D., et al. 1986. "Peritoneal Fluid Volume, Estrogen, Progesterone, Prostaglandin, and Epidermal Growth Factor Concentrations in Patients With and Without Endometriosis." Obstetrics and Gynecology 68: 189-94. Professional Journal

MEDLINE: Elevated **prostaglandin** (**PG**) levels in peritoneal fluid have been implicated as playing a role in infertility associated with endometriosis. This study was designed to measure peritoneal fluid levels of PG and other hormones that may influence PG release ... **Peritoneal fluid volume** and levels of **estrogen**, **progesterone**, and **epidermal growth factor** were significantly (P less than .05) increased during the secretory, as opposed to the proliferative, phase in both groups of patients, but no significant differences in these parameters were found between patients

with and without endometriosis during either the proliferative or secretory phases. Although **PG** levels did not vary during the menstrual cycle in either group of patients, all four **prostanoids** were present in significantly (P less than .05) higher concentrations in patients with endometriosis as compared with patients without endometriosis. Furthermore, increased **PG** levels in patients with endometriosis appear to be due primarily to an increase in **PG** levels during the secretory phase of the cycle.

Khoo, S.K., A. Brodie, and E.V. Mackay. 1986: "Peritoneal Fluid Biochemistry in Infertile Women with Mild Pelvic Endometriosis. Prognostic Value of Prostaglandin $F_{2\alpha}$ Concentration to Subsequent Pregnancy." Australian and New Zealand Journal of Obstetrics and Gynaecology 26: 210-15. Professional Journal

"Although the factors involved in the pathophysiology of endometriosis are probably multiple and interrelated, prostaglandins may play an important role in the infertility of women with mild disease. In the present study, prostaglandin $\mathbf{F}_{2\alpha}$ (PGF_{2 α}) and 17 β -oestradiol were measured in the peritoneal fluid of [27] infertile women who had mild pelvic endometriosis (without anatomical distortion) and compared with those values in [29] normal women who had no pelvic disease and in [11] women with pelvic infection. Although there was a wide scatter of PGF₂₀ values, the mean (1 066 pg/ml) in the endometriosis group was significantly greater than that in the other 2 groups (542 pg/ml, normal and 688 pg/ml, pelvic infection); the increase was found in both phases of the menstrual cycle. The mean concentration of 17 β -oestradiol was markedly higher in the luteal than the follicular phase in all 3 groups; however, no significant differences were found between the groups. Interestingly, the mean value of PGF_{2 α} and 17 β -oestradiol was higher in women with endometriosis who failed to conceive than in those who became pregnant. An estimation of PGF₂₀ in the peritoneal fluid may have prognostic value in the evaluation of infertile patients, especially those with mild endometriosis or in whom the problem is unexplained."

Badawy, S.Z., V. Cuenca, and L. Marshall. 1987. "Peritoneal Fluid Prostaglandins in Patients with Endometriosis." *Contributions to Gynecology and Obstetrics* 16: 60-65. Professional Monograph

The researchers studied peritoneal fluid prostaglandins in 15 women with endometriosis, 5 with unexplained infertility, and 5 controls.

They conclude: "**Prostaglandins** are increased in the peritoneal fluid of patients with endometriosis. The effect of these prostaglandins on ovarian function needs more studies. It appears that the main effect of prostaglandins on tubal and uterine functions leads to infertility."

Pungetti, D., et al. 1987. "Prostanoids in Peritoneal Fluid of Infertile Women with Pelvic Endometriosis and PID." *Acta Europaea Fertilitatis* 18: 189-92. Professional Journal MEDLINE: Peritoneal fluid collected at celioscopy in infertile subjects was assayed for **steroids** and several **prostanoids** (**PGE**₂, **PGF**₂, **TxB**₂, **LTB4**) as part of a study into [the] pathophysiology of the female reproductive tract. **Prostaglandins**, produced massively in the pelvis, might interfere with fertility through various mechanisms (alterations in the egg implantation, follicle genesis, luteinization as well as tubal disorders). Our study of 54 patients showed a marked increase only of **TxB**₂ out of the prostanoids assayed in overall endometriosis. In pelvic flogosis [phlogosis, or inflammation], peritoneal **LTB4** (and **TxB**₂) were considerably increased if related to controls. This would suggest their role in the ethiopathogenesis of unexplained infertility (in relation to these pathologic patterns).

Morita, M., et al. 1990. "Minimal and Mild Endometriosis. Nd:YAG Laser Treatment and Changes in Prostaglandin Concentrations in Peritoneal Fluid." *Journal of Reproductive Medicine* 35: 621-24. Professional Journal

direct link (entry)

"Recently, peritoneal fluid factors have come to be associated with infertility in minimal and mild endometriosis patients, and **prostaglandin** (**PG**) is suspected of being one of those factors. We use the Nd:YAG laser for treatment of endometriosis ... **Peritoneal fluid volume** and **PGE**₂ [**prostaglandin**] **concentrations** were found to be significantly higher [in 52 cases of minimal and mild endometriosis] than those in the control group ([11] tubal obstruction patients). Seven of 52 patients received second-look laparoscopy three months after Nd:YAG laser treatment; the **PG concentration** showed a tendency to decrease in many patients, and the **PGE**₂ **concentration** turned out to be insignificant. Within one year, 30 patients achieved pregnancy ...

"Our results led us to the conclusion that minimal and mild endometriosis leads to infertility from the suppression of tubal motility caused by increasing **PGE₂ concentrations** and that Nd:YAG laser treatment may lower the PG concentration in peritoneal fluid, thereby increasing the chance of pregnancy."

SEE ALSO "Reviews" and other subsections of "Peritoneal Fluid Factors" for further mention of prostaglandins.

Immune Factors

Wild, R.A., and C.A. Shivers. 1985. "Antiendometrial Antibodies in Patients with Endometriosis." *American Journal of Reproductive Immunology and Microbiology* 8 (July): 84-86. Professional Journal

"Sera from 42 patients complaining of infertility were evaluated by indirect immunofluorescence for the presence of **antibodies** to the endometrium. The presence or absence of antibodies was matched with the findings at laparoscopy. Of the 42 patients examined for infertility, 28 (66.7%) had laparoscopic findings that corresponded to the presence or absence of endometriosis. Of 28 patients with positive antibody tests, 24

(85.7%) were found to have endometriosis. No correlation between the degree of immunofluorescence and the clinical severity of endometriosis could be determined ...

"However, the presence of these antibodies may correlate more with the degree of infertility than the clinically apparent severity of the disease."

Hill, J.A., et al. 1988. "Characterization of Leukocyte Subpopulations in the Peritoneal Fluid of Women with Endometriosis." Fertility and Sterility 50: 216-22. Professional Journal

MEDLINE: Monoclonal antibodies identifying **leukocyte** subpopulations were applied to smears of laparoscopically collected peritoneal fluid **leukocytes** and parallel samples of peripheral blood **leukocytes** from [33] women with endometriosis, [9] with unexplained infertility, and [8] fertile controls ... The most significant elevations in total **leukocytes**, **macrophages**, **helper T lymphocytes** and **natural killer cells** were observed in women with stage I and II endometriosis ... The results from this study indicate that the peritoneal environment is immunologically dynamic and suggest that **cellular immune mechanisms** may contribute to reproductive failure in women with endometriosis and unexplained infertility.

Schneider, E.G., et al. 1989. "Absence of a Direct Effect of Recombinant Interleukins and Cultured Peritoneal Macrophages on Early Embryonic Development in the Mouse." Biology of Reproduction 40: 825-33. Professional Journal

no link (entry)

MEDLINE: On the basis of their recent studies, several researchers have suggested that the infertility associated with mild endometriosis is due to the alteration of peritoneal fluid, resulting in impairment of the viability of gametes or embryos. Elevated numbers of macrophages and lymphocytes have been reported in the peritoneal fluid of patients with endometriosis. Interleukin-1 (IL-1) a major product of activated macrophages and Interleukin-2 (IL-2), a product of most activated T-cells, have been postulated to play a role in the infertility associated with this disease, possibly by acting as direct embryotoxic agents. We have examined the effect of purified recombinant **IL-1** and **IL-2**, which are not species-specific. on in vitro development of mouse embryos. Both interleukins [-1 and -2] had no effect on development to the blastocyst stage or on early stages of implantation, as measured in vitro by attachment and outgrowth of blastocysts to fibronectin-coated dishes. Moreover, co-culture of mouse embryos with activated human peritoneal macrophages had no effect on embryogenesis. We conclude that neither IL-1, nor other products of human macrophages activated by lipopolysaccharide, nor IL-2 are directly toxic to early mouse embryonic development.

Hill, J.A., and D.J. Anderson. 1989. "Lymphocyte Activity in the Presence of Peritoneal Fluid from Fertile Women and Infertile Women With and

Without Endometriosis." American Journal of Obstetrics and Gynecology 161: 861-64. Professional Journal

"Peritoneal fluid from [41] women with endometriosis, [8] unexplained infertility, and [8] fertile controls were compared to one another and to normal human serum for effects on **lymphocyte** proliferation in vitro. Peritoneal fluid samples were also assayed for both **interleukin-1** and **interleukin-2** ...

"Our data indicate that peritoneal fluid from women with endometriosis and unexplained infertility support the activation and proliferation of **lymphocytes**. **Leukocyte** products may locally affect the progression of disease and fertility."

Inflammation and Autoimmune Response

Burke, R.K., A.T. Hertig, and C.A. Miele. 1985. "Prognostic Value of Subacute Focal Inflammation of the Endometrium, with Special Reference to Pelvic Adhesions as Observed on Laparoscopic Examination. An Eight-Year Review." Journal of Reproductive Medicine 30: 646-50. Professional Journal

"The significance of the endometrial lesion known as **subacute focal inflammation (SFI)** (or the more descriptive term lymphoid aggregates [LA]) as a factor in reproductive failure is controversial. We correlated the pelvic findings of 262 consecutive laparoscopic procedures performed for infertility with the histologic diagnosis from an endometrial biopsy that had been obtained previously as part of the infertility evaluations. Pelvic adhesions were observed in 87.3% of women in whom the diagnosis of SFI had been made. Pelvic adhesions were observed in only 10.9% of women whose biopsies did not contain SFI. Of women with SFI on biopsy but without pelvic adhesions, 70.6% demonstrated American Fertility Society stage I endometriosis at laparoscopy. These findings are statistically significant (P < 0.001) ...

"This study suggested an association between SFI and pelvic adhesions and possibly endometriosis."

Olive, D.L., A.F. Haney, and J.B. Weinberg. 1987. "The Nature of the Intraperitoneal Exudate Associated with Infertility: Peritoneal Fluid and Serum Lysozyme Activity." *Fertility and Sterility* 48: 802-806. Professional Journal

"An **intraperitoneal inflammatory process** has been associated with infertility in women without anatomic distortion of the pelvic viscera, particularly with endometriosis. This phenomenon was investigated by measuring **peritoneal fluid** (PF) and serum levels of a major secretory product of the **macrophage**, **lysozyme**, in [20 infertile women with endometriosis, 14 infertile women without endometriosis, and 12 fertile controls] undergoing laparoscopy ... Results suggest that a localized intraperitoneal inflammatory reaction is associated with infertility in the absence of anatomic distortion of the pelvic viscera ...

"This PF inflammatory exudate in infertile women appears to be confined within the abdomen because the serum lysozyme levels are not elevated. The stimulus responsible for eliciting this localized reaction is unknown, but the cyclic irritation of retrograde menstruation, with or without implanted endometrial cells, appears to be the most likely candidate."

Haney, A.F., and J.B. Weinberg. 1988. "Reduction of the Intraperitoneal Inflammation Associated with Endometriosis by Treatment with Medroxyprogesterone Acetate." *American Journal of Obstetrics and Gynecology* 159: 450-54. Professional Journal

"An **intraperitoneal inflammatory exudate** has been repeatedly observed in infertile women without mechanical compromise of the pelvic viscera, particularly with endometriosis. This is manifested by increases in the **peritoneal fluid volume**, **leukocyte number**, and **proteolytic enzyme concentrations**. We tested the hypothesis that the stimulus responsible for eliciting this **intraperitoneal inflammation** is retrograde menstruation by measuring the **peritoneal fluid volume** and **leukocyte count** in 16 infertile women with endometriosis [no control group] before and after ovulation suppression with medroxyprogesterone acetate, 30 mg/day for 4 months ...

"We conclude that medroxyprogesterone acetate treatment reduces the intraperitoneal exudate associated with endometriosis. These results support the contention that the stimulus eliciting the **intraperitoneal inflammation** in infertile women with endometriosis is retrograde menstruation."

Mathur, S., et al. 1988. "Endometrial Antigens Involved in the Autoimmunity of Endometriosis." *Fertility and Sterility* 50: 860-63. Professional Journal

"Serum and peritoneal fluid from five fertile women without endometriosis and serum (n=23) and peritoneal fluid (n=12) from infertile women with endometriosis were tested for the presence of **antibodies** against endometrial tissue antigens by a Western blot analysis." The researchers find that women with endometriosis have a heightened endometrial **autoimmunity** and conclude "that the humoral and local endometrial autoimmunity detected in patients with endometriosis is primarily directed against antigens with MW [molecular weights] of 26 and 34 kd."

SEE ALSO "Reviews" and other subsections of "Peritoneal Fluid Factors" for further mention of inflammation and autoimmune response.

Specific Immunity

Kreiner, D., et al. 1986. "Endometrial Immunofluorescence Associated with Endometriosis and Pelvic Inflammatory Disease." *Fertility and Sterility* 46: 243-46. Professional Journal

"Anti-immunoglobulin G (anti-IgG) staining in the endometrium by immunofluorescence has been associated with endometriosis. To

investigate this phenomenon further, we took endometrial samples from 42 patients who underwent laparoscopy or laparotomy, which were tested for immunofluorescence ... Of 18 patients with documented endometriosis, 16 had positive immunofluorescence (89% sensitivity). Of 24 patients with no evidence of endometriosis, 9 had false-positive immunofluorescence and 15 had negative immunofluorescence. Of the 9 false-positive samples, 8 had evidence of old pelvic inflammatory disease. In the absence of this condition, there was only one false-positive study for immunofluorescence. The implications of these findings in terms of the pathophysiology of endometriosis-associated infertility is that it may be an immune-mediated process."

Badawy, S.Z., et al. 1987. "Immune Rosettes of T and B Lymphocytes in Infertile Women with Endometriosis." *Journal of Reproductive Medicine* 32: 194-97. Professional Journal

"We examined the cell-mediated immune response in women with pelvic endometriosis by quantitating their **T and B lymphocytes**." Of 89 patients, aged 22-39, with infertility problems treated by laparoscopy, 43 were diagnosed with endometriosis and 46 with adhesions or tubal blockage. The latter were considered the control group. "The study was conducted on heparinized peripheral blood and peritoneal fluid. The results were compared with those [of the control group] ...

"The results demonstrated an increased number of **T** and **B** cells in peritoneal fluid and peripheral blood from patients with endometriosis as compared with controls. Furthermore, the ratio T4:T8 was significantly increased in patients with endometriosis. These results suggest a cell-mediated immune response in the presence of endometriosis."

Liu, J., et al. 1987. "The Immunological Study of Patients with Endometriosis." *Contributions to Gynecology and Obstetrics* 16: 66-72. Professional Monograph

no link - IgG, IgM, IgA, and C3

Researchers examined the peritoneal fluid of 57 patients with endometriosis, aged 26-40 years, and 20 age-matched subjects with normal fertility. "The mean **volumes of peritoneal fluid** recovered from patients with endometriosis were larger than those of normal controls" by a statistically significant difference. "The serum concentrations of **IgG, IgM, IgA** and **C3** ... were about the same" in the two groups; "the peritoneal fluid concentrations of the **immunoglobulins** and **complement C3** were all somewhat increased" in the women with endometriosis. "Only the increase of **IgA** was of statistical significance." In an "immunofluorescence assay for **immunoglobulins** and **complement** in biopsied endometria," women with endometriosis "showed a very significant increase in the proportion of endometria that contained glands and stromal tissue staining quite strongly by immunofluoresence for **immunoglobulins** and **C3** [**complement 3**]." In radioimmunoassay, "the serum concentrations and the peritoneal concentrations of **PGF**₂₀ **metabolite** of the patients with endometriosis

exceeded that of normal controls." Conclusion: "The results of our study do tend to support ... possible association of the immunological aspects of endometriosis and low fertility."

Bartosik, D., et al. 1987. "Immunoproteins in the Endometrium: Clinical Correlates of the Presence of Complement Fractions C3 and C4."

American Journal of Obstetrics and Gynecology 156: 11-15.

Professional Journal

"The presence of **complement fractions C3 and C4** in endometrial tissue was studied in a consecutive series of [67] patients undergoing diagnostic laparoscopy, to determine their specific association with endometriosis ...

"Among patients with endometriosis and infertility, **complement** was much more likely to be found in patients with primary infertility than in those with secondary infertility (p < 0.007)."

Meek, S.C., D.D. Hodge, and J.R. Musich. 1988. "Autoimmunity in Infertile Patients with Endometriosis." *American Journal of Obstetrics and Gynecology* 158: 1365-73. Professional Journal

"General and specific immune function was studied in [20] infertile patients with endometriosis and in [20] controls with proved fertility and absence of pelvic pathology. [The mean ages of the patient and control groups were 31.8 and 33.6 years, respectively.] General nonspecific parameters studied included serum IgG, IgA, IgM, C3, C4, and total complement levels. Immunofluorescence and Ouchterlony immunodiffusion techniques were used to study specific immune function by assaving for endometrial antibodies in serum and peritoneal fluid. Peritoneal fluid volume was also assessed. IgA levels were decreased in infertile patients with endometriosis, IgG, C3, and C4 levels were also decreased in the follicular phase of the menstrual cycle in these patients. The volume of peritoneal fluid was increased in these patients and a significant number of these had low C4 levels. The immunodiffusion studies identified antiendometrial antibodies in the serum and peritoneal fluid in infertile patients with endometriosis. This study has shown that the **immune system** is altered in infertile patients with endometriosis."

Badawy, S.Z., et al. 1989. "The Regulation of Immunoglobulin Production by B Cells in Patients with Endometriosis." *Fertility and Sterility* 51: 770-73. Professional Journal

MEDLINE: Nineteen patients with endometriosis and 26 control infertile patients were included in [a study] conducted on sterile heparinized peripheral blood and peritoneal fluid. The age range was 20 to 37 years for both groups ... Increased amounts of **immunoglobulin (Ig) IgG and IgA** were demonstrated in the peritoneal cell cultures (P less than 0.05), whereas peripheral blood cell cultures showed only an increase in **IgG** in patients with endometriosis (P less than 0.05). There was an increase in the number of **T cells**, **B cells**, and the ratio of CD4/CD8 **lymphocytes** in

endometriosis compared with control patients (P less than 0.005) in both peritoneal fluid and peripheral blood. This study suggests that **immuno-globulin** production by the activated **B cells** may be regulated by the increased presence of **T cells**, specifically the helper cells (CD4) in endometriosis.

Gleicher, N., et al. 1989. "Reproductive Failure Because of Autoantibodies: Unexplained Infertility and Pregnancy Wastage." *American Journal of Obstetrics and Gynecology* 160: 1376-80; discussion 1380-85. Professional Journal

Excerpta Medica: Abnormal poplyclonal **B cell** activation has been demonstrated in patients with endometriosis. To determine whether the noted **B cell** abnormalities were primarily a feature of the disease endometriosis or its manifestations of infertility and pregnancy wastage, we investigated antibody profiles in 26 female patients with unexplained infertility (group A) and 24 patients with unexplained pregnancy wastage (group B) but without documented endometriosis.

We conclude that some patients with unexplained infertility and pregnancy wastage suffer from polyclonal **B cell** activation. It is therefore tempting to speculate that autoantibody abnormalities may be causally related to infertility and pregnancy loss.

Isaacson, K.B., et al. 1990. "Endometrial Synthesis and Secretion of Complement Component-3 by Patients With and Without Endometriosis." Fertility and Sterility 53: 836-41. Professional Journal

"In the present study we examined **complement-3 (C3)** synthesis and secretion from early proliferative endometrium of [23] infertile patients with and without endometriosis ... Patients with minimal endometriosis produced significantly greater amounts of endometrial **C3** than patients with no endometriosis or patients with severe endometriosis."

SEE ALSO "Reviews" and other subsections of "Peritoneal Fluid Factors" for further mention of specific immune factors.

Non-Specific Immunity

Olive, D.L., J.B. Weinberg, and A.F. Haney. 1985. "Peritoneal Macrophages and Infertility: The Association Between Cell Number and Pelvic Pathology." *Fertility and Sterility* 44: 772-77. Professional Journal

MEDLINE: Increased numbers of peritoneal **macrophages** have been repeatedly associated with infertility. Because the factors contributing to this intraperitoneal exudate are unknown, this study was carried out to determine which anatomic or endocrinologic abnormalities in infertile women might be associated with an increase in leukocyte numbers. The peritoneal fluid from 103 women was analyzed. Nonparametric data analysis demonstrated significantly greater cell counts in infertile women with endometriosis, compared with other infertile women (P less than 0.01) or fertile control subjects (P less than 0.005). Multiple regression analysis

was then used to determine the relationship of individual variables to cell number without the influence of confounding factors. These data demonstrate that the best correlation with elevated **macrophage** number is in women who have infertility and no mechanical fertility factors (of which mild endometriosis is a subgroup). Thus, an increase in peritoneal **macrophage** number is not restricted to women with endometriosis but, rather, is seen in a subset of infertile women generally without mechanical or endocrinologic infertility factors.

Chacho, K.J., et al. 1986. "Peritoneal Fluid in Patients With and Without Endometriosis: Prostanoids and Macrophages and Their Effect on the Spermatozoa Penetration Assay." American Journal of Obstetrics and Gynecology 154: 1290-99. Professional Journal

MEDLINE: Peritoneal fluid from 35 women with endometriosis and from 34 control women was aspirated at laparoscopy and analyzed. No differences in **prostanoid levels** were found. The **peritoneal fluid volume**, **macrophage** concentration, **macrophage** content, and content of activated **macrophages** as measured by acid phosphatase staining were all significantly elevated in the endometriosis patients. The **macrophages** were incubated and the medium was added to the zona-free hamster egg sperm penetration assay. This medium caused a significant decrease in the percentage of ova penetrated in this assay. It is postulated that one of the mechanisms of infertility in women with endometriosis may involve the increased number of activated **macrophages** and their ability to interfere with **sperm-egg interaction**.

Fazleabas, A.T., F.S. Khan-Dawood, and M.Y. Dawood. 1987. "Protein, Progesterone, and Protease Inhibitors in Uterine and Peritoneal Fluids of Women with Endometriosis." *Fertility and Sterility* 47: 218-24. Professional Journal

"Because **progesterone** (P) has been shown to have a stimulatory effect on protein secretion by the human endometrium in vitro and **plasma protease inhibitors** have been implicated to be associated with **inflammation** and **proteolytic equilibrium** during implantation ... This study was undertaken to determine whether women with endometriosis have altered **protein**, **progesterone** (P), and **protease inhibitor concentrations** in their uterine fluid and peritoneal fluid (PF) compared with controls at different phases of the menstrual cycle." The researchers examined "29 normal women" and 16 women diagnosed with endometriosis.

"Results indicate that women suffering from endometriosis have ... significantly lower levels of **P** and less **protease inhibitor** within their uterine cavity during the luteal phase of the cycle, and ... significantly higher concentrations of **protein** and **protease inhibitor** in PF during the luteal phase." The researchers conclude that "these alterations within the uterine lumen and peritoneal cavity of these women may contribute to their inability to conceive." The higher concentrations of **protease inhibitors** might be responsible for inhibiting **plasmin** produced by **macrophages** as part of the **inflammatory response**. This might account for decreased

counts of plasminogen activator activity in the peritoneal fluid of women with endometriosis.

Fakih, H., et al. 1987. "Interleukin-1: A Possible Role in the Infertility Associated with Endometriosis." *Fertility and Sterility* 47: 213-17. Professional Journal

"This study was undertaken to evaluate the role of **Interleukin-1** in the infertility associated with mild endometriosis." Peritoneal fluid (PF) was obtained at laparoscopy from 11 patients with minimal or mild endometriosis and from 7 control women with normal fertile cycles undergoing tubal ligation.

"In conclusion, **IL-1** activity is present in the PF of infertile women with endometriosis and is absent in the PF of normal fertile women. Furthermore, peritoneal **macrophages** obtained from patients with endometriosis, but not from normal fertile women, secrete **IL-1** in culture. This latter finding supports earlier reports of increased activation of peritoneal **macrophages** in patients with endometriosis. **IL-1** was also found to be toxic to the growth of 2-cell mouse embryos in vitro. Because of the multitude of effects that **IL-1** mediates and in view of our findings, it seems that **IL-1** might be an important factor in the pathophysiology of and in the infertility secondary to endometriosis."

Zeller, J.M., et al. 1987. "Enhancement of Human Monocyte and Peritoneal Macrophage Chemiluminescence Activities in Women with Endometriosis." *American Journal of Reproductive Immunology and Microbiology* 13 (March): 78-82. Professional Journal

MEDLINE: Preliminary reports indicate that products of human mononuclear phagocytes may contribute to the infertility associated with endometriosis. To determine whether the generation of reactive oxygen metabolites by blood monocytes and peritoneal macrophages is altered in women with endometriosis, the present study evaluated luminol-enhanced chemiluminescence (CL) in cells at rest and following stimulation with phorbol myristate acetate (PMA) or serum-opsonized zymosan (SOZ). Peripheral venous blood and peritoneal fluid samples were collected from 60 infertile women undergoing diagnostic laparoscopy at midluteal phase and mononuclear phagocytic cell fractions were obtained by density gradient centrifugation ... It appears that chronic stimulation of macrophages in the peritoneal cavity provokes constitutive release of large quantities of reactive oxygen products in women with endometriosis. This may occur secondary to the accumulation of activated monocytes into the peritoneal cavity.

Halme, J., S. Becker, and S. Haskill. 1987. "Altered Maturation and Function of Peritoneal Macrophages: Possible Role in Pathogenesis of Endometriosis." American Journal of Obstetrics and Gynecology 156: 783-89. Professional Journal

"Human peritoneal macrophages from healthy women and patients with endometriosis were analyzed with flow cytometry for size distribution. cell membrane antigen expression, and membrane function." One hundred and two fertile women and 223 patients with various causes of infertility were studied. Note: The number of women with endometriosis is not specified.

"Endometriosis was associated with a significantly increased number of peritoneal macrophages and a higher proportion of large macrophages with increased expression of three antigen markers. macrophages from normal patients exhibited diminished cell membrane capping function as compared with that of endometriosis-related macrophages or blood monocytes. On the basis of these findings, a hypothesis is formulated suggesting that endometriosis is associated with an increased influx of macrophages that are allowed to undergo further maturation-activation. The resultant population of large macrophages may contribute to the maintenance of the disease or associated infertility."

In a concluding "Questions and Answers," Dr. Halme remarks that it is as yet unknown whether endometriosis causes the effect on macrophages, or macrophages on endometriosis.

Leroy, J.-L., P. Saint-Pol, and E. Hermand. 1987. "PAS-Stained Macrophages in Peritoneal Fluid of Women with Endometriosis." Contributions to Gynecology and Obstetrics 16: 164-69. Professional Monograph

no link - volume of peritoneal fluid

Researchers collected peritoneal fluid from 275 women undergoing laparoscopy for sterility or pelvic pain, and 25 women for tubal microsurgery. Ninety-five had a normal pelvis, 88 had subacute or chronic inflammatory disease (PID), and 117 had endometriosis. During the follicular phase, women with endometriosis had a greater volume of peritoneal fluid, but during the luteal phase there was no statistical difference among the three groups. The same cell population was found in each group. In a cell count, "the total amount of macrophages seems to be more important in the endometriosis group mainly because of an increase of the fluid volume. Nevertheless, statistical analysis [did] not show any significant difference." Study "results suggest that concentration of macrophages is constant in infertile patients and that a possible increase of total macrophages in endometriosis is a reflection of the increase of pelvic fluid volume."

Awadalla, S.G., et al. 1987. "Local Peritoneal Factors: Their Role in Infertility Associated with Endometriosis." American Journal of Obstetrics and Gynecology 157: 1207-14. Professional Journal

no link — macrophages

MEDLINE: To detect peritoneal abnormalities that could account for infertility associated with endometriosis, 122 infertile individuals were studied at the time of laparoscopy for diagnostic purposes or for in vitro

fertilization. Four groups were defined: group 1, laparoscopy without endometriosis; group 2, laparoscopy with endometriosis; group 3, in vitro fertilization without endometriosis; and group 4, in vitro fertilization with endometriosis. Mean **peritoneal fluid volume** was greater, although not significantly so, in group 4 (29.0 \pm 6.6 ml, mean \pm SEM) than in group 3 (18.2 \pm 2 ml). The concentration and total number of pelvic **macrophages** were similar for groups 1 and 2. The total number of pelvic **macrophages** was increased in group 4 (16.9 \pm 4.2 \times 10(6)) versus group 3 (10.0 \pm 1.8 \times 10(6)) (p = 0.08). The mean **sperm phagocytosis** in vitro did not differ among the four groups studied. **Interleukin 1** activity within the peritoneal fluid and the in vitro interleukin 1 production rate did not differ between individuals with and without endometriosis. **Peritoneal fluid** and **macrophage** supernatants from individuals with endometriosis were not embryotoxic when studied in an in vitro mouse embryo system.

Chacho, K.J., P.J. Andresen, and A. Scommegna. 1987. "The Effect of Peritoneal Macrophage Incubates on the Spermatozoa Assay." *Fertility and Sterility* 48: 694-96. Professional Journal

MEDLINE: **PFM [Peritoneal fluid macrophages]** have been implicated as a possible cause of infertility in endometriosis. Previous work from our laboratory has indicated that medium incubated with PFM caused a significant decrease in sperm penetration when added to the sperm penetration assay (SPA). To further delineate this finding, medium incubated with killed macrophages, heat-inactivated medium, and various concentrations of macrophage media were added to the SPA ... We conclude that medium incubated with PFM is capable of decreasing **sperm penetration** as measured in the SPA in a dose-dependent fashion. Furthermore, the substance responsible for this decrease appears to be heat-stable and released from dead as well as live macrophages.

Hoffman, M., A.F. Haney, and J.B. Weinberg. 1988. "Reduced Trypsin-Binding Capacity of α_2 -Macroglobulin in the Peritoneal Fluid of Women with Endometriosis: Possible Relevance to Alterations in Macrophage Function." Fertility and Sterility 50: 39-47. Professional Journal

" α_2 -macroglobulin (α_2M) is a plasma protein with proteinase inhibitor and immune modulatory capabilities. The amounts of α_2M in peritoneal fluid (PF) from [8] women with endometriosis and [7] women with noninflammatory gynecologic conditions were analyzed by functional (trypsin binding) and immunologic assays. The most important finding of this study was that a significant amount of the α_2M in the peritoneal fluid of patients with endometriosis had been inactivated by an as yet undetermined mechanism. It is possible that decreased proteinase-binding ability of α_2M may play a role in the pathogenesis of endometriosis and associated infertility by decreasing negative feedback control of macrophage activities."

Halme, J., et al. 1988. "Peritoneal Macrophages from Patients with Endometriosis Release Growth Factor Activity In Vitro." Journal of Clinical Endocrinology & Metabolism 66: 1044-49. Professional Journal

"We studied the *in vitro* secretion of **macrophage-derived growth factor (MDGF)** activity by peritoneal macrophages from fertile and infertile women. Peritoneal fluid was obtained from 55 women undergoing laparoscopy for evaluation and treatment of infertility or for tubal sterilization. Among the 55 women, **macrophages** from 10 of 36 (28%) women with normal pelvic anatomy or tubal occlusion/pelvic adhesions released significant **MDGF** activity. In contrast, **macrophages** from 13 of 19 (68%) women with endometriosis, a significantly higher proportion (P < 0.02), released **MDGF**. The finding that endometriosis is associated with *in vivo* primed peritoneal **macrophages** that produce **MDGF** *in vitro* may help to explain the proliferation or maintenance of endometrial tissue in the peritoneal cavity." (Note: The researchers do not discuss the implications for infertility.)

Dunselman, G.A.J., et al. 1988. "Functional Aspects of Peritoneal Macrophages in Endometriosis of Women." *Journal of Reproduction and Fertility* 82: 707-10. Professional Journal

MEDLINE: Peritoneal fluid was collected in the periovulatory phase of the cycle from 25 women undergoing laparoscopy. Endometriosis was diagnosed in 13 patients [9 with stage 1 and 4 with stage 2 of the American Fertility Society's classification of endometriosis] and 12 patients without endometriosis served as controls. In endometriosis patients the total **peritoneal fluid cell number and cell concentration** was significantly higher than in controls, indicating peritoneal irritation by endometrial implants. Peritoneal fluid **macrophages** in patients with endometriosis showed significantly increased erythrophagocytosis and lower chemiluminescence than in controls, suggesting an advanced differentiation of the macrophages in endometriosis patients. The macrophages in this stage of differentiation may interfere with gametes and embryos and thus contribute to endometriosis-associated subfertility.

Samejima, T., et al. 1989. "Activity of Peritoneal Macrophages in Endometriosis." *Asia Oceania Journal of Obstetrics and Gynaecology* 15: 175-81. Professional Journal

MEDLINE: It is thought that peritoneal **macrophages** increase in number in women with endometriosis and that the macrophages phagocytize sperm or the fertilized ovum, leading to infertility. We examined the levels of **phagocytosis** by peritoneal **macrophages** in patients with and without endometriosis using a flow cytometric assay. The level of **phagocytosis** in the control group was significantly lower than in the group with endometriosis. Quantitative results on the level of **phagocytosis** by peritoneal **macrophages** suggest that peritoneal **macrophages** are one of the factors contributing to infertility associated with endometriosis.

Laitl, J., et al. 1989. "Peritonealni macrofagy a jejich activita u sterilnich pacientek s endometriozou." ["Peritoneal Macrophages and Their Activity in Sterile Patients with Endometriosis."] Ceskoslovenska Gynekologie 54: 667-72. Language: Czechoslovakian. Professional Journal

no link - phagocytic activity

MEDLINE: The authors analyzed the **peritoneal fluid (PF)** during laparoscopic examination in 50 sterile women, including 27 where endometriosis was found. The control group was formed by 23 sterile women without signs of endometriosis ... In the group of sterile women with endometriosis there was significantly increased **volume of PF**, higher concentration and absolute number of **macrophages** than in the group of patients without endometriosis. The **phagocytic activity** of peritoneal macrophages did not differ significantly in the control group and in patients with endometriosis.

Gentry, W.L., et al. 1989. "Failure to Demonstrate Significant Antisperm Antibodies in Peritoneal Fluid of Patients with Endometriosis." Fertility and Sterility 52: 949-52. Professional Journal

no link (entry)

MEDLINE: In light of possible increases in serum autoimmune antibodies, increased peritoneal macrophages, and increased sperm phagocytosis associated with this disease, we postulated that peritoneal fluid antisperm antibodies would be increased and might be the cause of increased **sperm phagocytosis** and its associated infertility. Peritoneal fluid, from 18 patients with endometriosis and 10 infertile controls, was tested with the antisperm antibody immunobead test validated for peritoneal fluid. One of 18 patients with endometriosis and none of 10 controls had **antisperm antibodies** present. Therefore, increased **sperm phagocytosis** is unlikely a result of peritoneal **antisperm antibodies** in endometriosis patients.

SEE ALSO "Reviews" and other subsections of "Peritoneal Fluid Factors" for further mention of nonspecific immune factors.

Tumour Necrosis Factor (TNF)

Eisermann, J., et al. 1988. "Tumor Necrosis Factor in Peritoneal Fluid of Women Undergoing Laparoscopic Surgery." *Fertility and Sterility* 50: 573-79. Professional Journal

"The level of **tumor necrosis factor (TNF) in peritoneal fluid (PF-TNF)** of 74 women [aged 17-43, 46 with endometriosis] undergoing laparoscopy was determined. The difference between the mean concentration of PF-TNF of women with normal pelvic anatomy and women with moderate or severe endometriosis was significant (P < 0.01). The proportion of PF-TNF-positive women with PID and those with moderate or severe endometriosis was also significantly higher when compared to women with normal pelvic anatomy (P < 0.05; P < 0.02). The proportion of PF-TNF

positive women among nulligravid and nulliparous women was significantly higher than that of women with two or more pregnancies (P < 0.01) and two or more deliveries (P < 0.005). These results indicate that the presence of PF-TNF is associated with primary infertility and endometriosis."

Eisermann, J., et al. 1989. "The Effect of Tumor Necrosis Factor on Human Sperm Motility In Vitro." Journal of Andrology 10: 270-74. Professional Journal

"**Tumor necrosis factor (TNF alpha)** is present in elevated levels in peritoneal fluid from infertile women with endometriosis ...

"This study addresses the *in vitro* effect of TNF α on sperm motility using both peritoneal fluid containing high levels of TNF α from women with endometriosis, and recombinant TNF α at levels similar to those found in these fluids. The results show that sperm motility is significantly reduced by peritoneal fluids containing TNF α as well as by recombinant TNF α . The ability of anti-TNF α to block the inhibition of sperm motility by peritoneal fluids indicates not only that TNF α mediates the inhibition, but that under these experimental conditions TNF α is the primary factor responsible for the loss of sperm motility ...

"Although it is difficult to extrapolate from *in vitro* experiments to the *in vivo* situation, the data presented here support the hypothesis that TNF α may play a role in the infertility associated with endometriosis by inhibiting sperm motility."

Halme, J. 1989. "Release of Tumor Necrosis Factor-α by Human Peritoneal Macrophages In Vivo and In Vitro." American Journal of Obstetrics and Gynecology 161: 1718-25. Professional Journal

"Tumor necrosis factor is a product of activated monocytes, macrophages, and lymphocytes that exerts a variety of effects in the host. Its cytotoxicity toward gametes has been suggested as a mechanism of how activated macrophages may cause subfertility, inasmuch as detectable levels of tumor necrosis factor have been reported in the peritoneal fluid of infertile patients. To further examine this issue we measured tumor necrosis factor activity in peritoneal fluid and its release in vitro from monocytes or peritoneal macrophages of [78 patients, aged 23-42, 34 with endometriosis] undergoing laparoscopy because of either tubal ligation or infertility ...

"Statistical analysis of **tumor necrosis factor** activity in peritoneal fluid in various diagnostic categories revealed a significantly elevated level in patients with endometriosis, as compared with fertile women. Endometriosis and pelvic adhesions were also significantly more likely to be associated with measurable levels of **tumor necrosis factor** activity released by peritoneal **macrophages** in vitro."

Appendix

A search of MEDLINE in January 1993 for publications in the years 1991 and 1992 produced the following articles on the physiological links between endometriosis and infertility. They are listed chronologically.

- Arumugam, K. 1991. "Serum Prolactin Levels in Infertile Patients with Endometriosis." *Malaysian Journal of Pathology* 13 (June): 43-45.
- Brosens, I. 1991. "Endometriosis Related to Infertility." *Current Opinion in Obstetrics and Gynecology* 3: 205-10.
- Colacurci, N., et al. 1991. "Immune System and Endometriosis." Acta Europaea Fertilitatis 22: 161-62.
- Mahmood, T.A., and A. Templeton. 1991. "Folliculogenesis and Ovulation in Infertile Women with Mild Endometriosis." *Human Reproduction* 6: 227-31.
- Mahmood, T.A., I.E. Messinis, and A. Templeton. 1991. "Follicular Development in Spontaneous and Stimulated Cycles in Women with Minimal-Mild Endometriosis." *British Journal of Obstetrics and Gynaecology* 98: 783-88.
- Mitkin, V.V., V.I. Kulakov, and G.T. Sukhikh. 1991. ["Peritoneal Fluid Immunologic Parameters in Endometriosis."] Akusherstvo I Ginekologiia 6 (June): 6-10.
- Vigano, P., et al. 1991. "Deficient Antiendometrium Lymphocyte-Mediated Cytotoxicity in Patients with Endometriosis." *Fertility and Sterility* 56: 894-99.
- Villalobos, M. 1991. "Myth and Realities about the Follicle Which Does Not Release the Ovum and Minimal Endometriosis." *Ginecologia y Obstetricia de Mexico* 59: 255-56.
- Wild, R.A., et al. 1991. "F(ab')₂ Segment Is the Active Component of Immunoglobulin G Autoantibody Generation in Patients with Endometriosis." *Fertility and Sterility* 56: 900-903.
- Bancroft, K., C.A. Vaughan Williams, and M. Elstein. 1992. "Pituitary-Ovarian Function in Women with Minimal or Mild Endometriosis and Otherwise Unexplained Infertility." *Clinical Endocrinology* 36: 177-81.
- Dodds, W.G., et al. 1992. "The Effect of Preovulatory Peritoneal Fluid from Cases of Endometriosis on Murine In Vitro Fertilization, Embryo Development, Oviduct Transport, and Implantation." American Journal of Obstetrics and Gynecology 166: 219-24.
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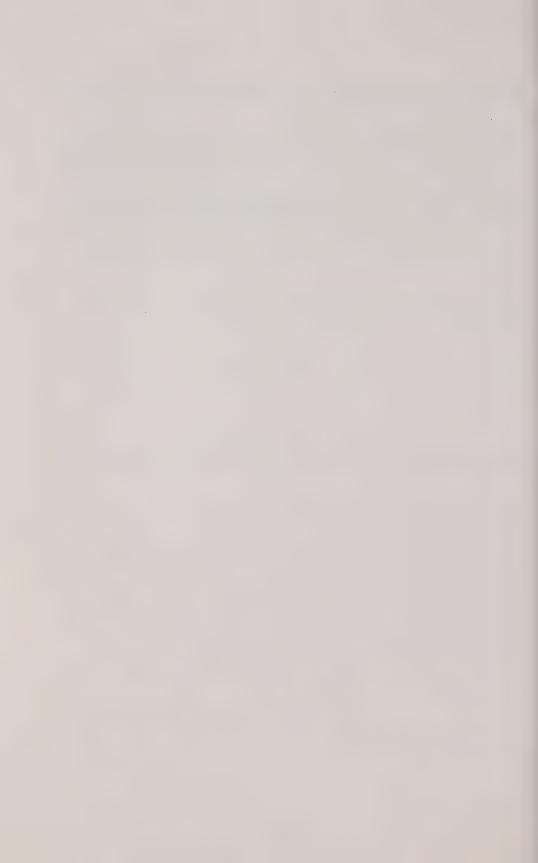
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The Impact of Medical Procedures on Fertility

Sylvie Dumas, Édith Guilbert, and Jacques-É. Rioux



Executive Summary

This study surveys the literature dealing with the risk of infertility resulting from acts prescribed or carried out by a physician, after surgical or other procedures on women or men for diagnostic, preventive, or treatment purposes. It analyzes the link between infertility and these procedures, as well as the risk of infertility arising from possible complications.

The study is divided into five parts. The first offers a definition of "infertility resulting from medical intervention." Infertility is defined as diminished capacity or incapacity to conceive during a given period of time or to carry a pregnancy to term and give birth to a healthy live child. The period of time before a physician makes a diagnosis of infertility is one year in North America and two years in Europe. Infertility can be the desired result of a medical procedure, such as a tubal ligation, or it can be an undesired outcome.

The second part provides a brief overview of infertility. It is estimated that between 10 and 15 percent of American couples are

This paper was completed for the Royal Commission on New Reproductive Technologies in February 1992.

infertile.* Between 1960 and 1975, the fertility rate in the United States dropped by 45 percent. However, the number of consultations for infertility is on the rise.

Age is one of the most important factors affecting infertility. The average age at first pregnancy has continued to rise in recent years. In addition, frequency of intercourse decreases with age, and this affects a couple's fertility.

The third part of the study deals with procedures that directly affect fertility, such as surgery on the reproductive organs. In this case, the risk of infertility is linked to surgery performed to re-establish fertility. In women, tubal re-anastomosis carries a risk of an ectopic pregnancy two to ten times that in women who have not had such surgery. The conception rate after this operation is about 60 percent. In men, vasovasostomies result in a conception rate ranging between 39 and 78 percent.

The fourth part discusses surgical procedures and tests that may result in pregnancy loss. Studies indicate a spontaneous abortion rate of 0.5 percent after amniocentesis, and the rate is higher in the case of chorionic biopsy. Cordocentesis has a risk of between 1 and 2 percent of *in utero* death, particularly for fetuses that are already stressed. No study shows a link between these three techniques and subsequent sterility.

In general, if infertility relating to these procedures occurs, it is after salpingitis. After a first occurrence of salpingitis, the infertility rate is thought to be 12.8 percent, after a second occurrence, 23 percent, and after a third, 54 percent.

A hysterosalpingography can affect fertility because of complications, particularly infection. The risk of acute salpingitis may be between 0.3 and 3.1 percent, and it can lead to infertility.

The risk of pregnancy among women fitted with an intrauterine contraceptive device (IUD) is between 0.5 and 2.0 per 100 woman-years. If pregnancy occurs, the risk of spontaneous abortion is about 50 percent with the IUD in place, and about 25 percent if it is removed. The risk of salpingitis relating to IUD use is between 8.3 and 78.7 percent for the Dalkon Shield® and between 1.5 and 10.8 percent for other models. It is not possible to establish a causal link between the use of IUDs and infertility, but their use by women at risk for salpingitis and sterility can lead to these problems.

Rarely, an induced abortion can cause infertility because of a secondary hysterectomy (0.9 per 10 000 in Canada), endometrial synechia (extremely rare, and curable), or acute salpingitis. According to studies, the rate of acute salpingitis is between 0.18 and 5 percent. The occurrence of this condition is influenced by a woman's history of sexually transmitted diseases and salpingitis. Repeated abortions may subsequently be associated with spontaneous abortion or premature

^{*} Please see C.S. Dulberg and T. Stephens, "The Prevalence of Infertility in Canada, 1991-1992: Analysis of Three National Surveys," in *The Prevalence of Infertility in Canada*, vol. 6 of the research studies, for the best estimate available for the Canadian population, published after this paper was received. It found that 7% of Canadian couples between ages 18 and 44 had not had a pregnancy after two years of cohabiting without contraception.

delivery, perhaps due to the method of abortion (dilatation and curettage).

The fifth part of the study comprises a discussion and a number of recommendations. In the discussion, the authors observe that there are few studies on the causal links between infertility on the one hand and surgical procedures or diagnostic tests on the other. From a methodological point of view, it is difficult to study complications, because a number of factors come into play.

The authors recommend that:

- 1. procedures and tests be used in accordance with precise protocols or indications;
- 2. neglected topics be studied, such as regret after a vasectomy, the effectiveness and safety of new contraceptive methods, and the long-term complications of surgical procedures on the cervix and of repeated induced abortions; and
- mechanisms be developed to publicize the advantages and disadvantages of medical procedures and their impact on fertility. These topics should be discussed when a couple consents to such procedures.

Introduction

Human infertility is a complex and multidimensional issue. Included in the terms of reference of the Royal Commission on New Reproductive Technologies is the mandate to measure human fertility, to gain an understanding of it, and to identify preventive measures. Research into the causes of infertility and their inter-relations has shown that this is an important issue. Among the risk factors for infertility, previous medical interventions were of obvious interest, and the Royal Commission wanted to find out more about the possible relationships between such interventions and infertility.

This is the background to this report on the impact of medical procedures on fertility, commissioned in May 1991 by the Royal Commission on New Reproductive Technologies. This report discusses the risk of infertility resulting from actions prescribed or performed by doctors, that is, following surgical and other procedures used for diagnostic, preventive, or curative purposes on men and women. Given the types of procedures to be researched, it is necessary not only to analyze links between these and infertility, but also to determine whether complications that might stem from such procedures involve an infertility risk factor. Although the Royal Commission requested a survey of the literature on this subject from 1980 on, this report surveys available scientific literature both before and after the 1980s.

This document comprises five parts. The first two define "infertility resulting from medical intervention" and give a brief summary of the infertility issue. The third part discusses procedures that have a direct

impact on fertility, including voluntary sterilization, and data are provided concerning hysterectomy rates, indications for hysterectomy, and alternative therapies. Other surgical procedures and tests that do not have a direct effect on fertility are considered in the fourth part, which surveys the literature on short- and long-term complications of such procedures. Lastly, the fifth part reflects on the issue, discusses the options, and presents recommendations.

The authors trust that this report will be useful to the Royal Commission in its mandate of updating knowledge on the human infertility issue. They also hope that it will help to shed light on the many concerns felt by the general public about medical procedures and will generate constructive reflection on such matters.

Definitions

Infertility is defined as either experiencing difficulties or being unable to conceive or to fertilize the ovum within a certain time-frame, or experiencing difficulties or being unable to complete a pregnancy and to give birth to a healthy living child.* Depending on the definition adopted, a diagnosis of infertility is made at anywhere from 12 to 24 months of unprotected intercourse. In North America one year is generally used, whereas in Europe two years is more common (Cohen and Palmer 1979).

Infertility can stem from medical action. On the one hand, the effect can be intentional and desirable, as in the case of a tubal ligation or a hysterectomy; on the other, it can be indirect and undesirable, as in the case of diagnostic or therapeutic action.

"Primary infertility" refers to a woman who is nulligravid, that is, a woman who has never been pregnant. "Secondary infertility" refers to a woman who has already been pregnant, but who cannot become pregnant again (Reiter and Buttram 1985).

Current Status

It is estimated that 10 to 15 percent of couples in the United States are infertile (Reiter and Buttram 1985).** The probability of infertility decreases as the period of unprotected intercourse for couples increases. This was shown in the research carried out by Guttmacher (1956), which

^{*} Definitions supplied by the Royal Commission on New Reproductive Technologies.

^{**} Please see C.S. Dulberg and T. Stephens, "The Prevalence of Infertility in Canada, 1991-1992: Analysis of Three National Surveys," in *The Prevalence of Infertility in Canada*, vol. 6 of the research studies, for the best estimate available for the Canadian population, published after this paper was received. It found that 7% of Canadian couples between ages 18 and 44 had not had a pregnancy after two years of cohabiting without contraception.

reports a gradual increase in the percentage of pregnancies as the period of unprotected intercourse increases, in the absence of any pathology in a man and a woman having normal sexual relations (Table 1).

Table 1. Relationship Between Percentage of Pregnancies and Duration of Period of Unprotected Intercourse

Exposure (months)	Cumulative incidence of pregnancy (%)
3	57
6	72
12	85
24	93

Is infertility a problem that is growing? Whereas the fertility rate in the United States from 1957 to 1967 was 123/1 000 woman-years (women from 15 to 44 years of age), it had declined to 67/1 000 by 1975 (Reiter and Buttram 1985). This significant decline in the fertility rate may be attributed to a number of phenomena, including:

- increase in the cost of living;
- women entering the labour market and their desire for a career;
- the availability of effective contraceptive methods;
- the liberalization of abortion;
- the male factor (decrease in sperm quality);
- the spread of sexually transmitted diseases (STDs); and
- late marriages and pregnancies (Reiter and Buttram 1985).

Such decline in the fertility rate is a reflection of a desire to have fewer children, not to have no children. The problem of infertility generally appears when couples attempt to have a first child, which explains why there is no decrease in the number of infertility consultations, but rather an increase.

Among the factors that affect fertility, age is certainly one of the most important. The average age of first-time mothers has continually increased in recent years (Reiter and Buttram 1985). Delaying motherhood gives pathologies (myoma, endometriosis, etc.) associated with infertility a longer period in which to emerge. Fertility also declines naturally with age, particularly after 40 years. In a French study on the pregnancy rate one year after artificial insemination (which eliminates any bias resulting from frequency of intercourse), researchers reported a pregnancy rate of 74 percent in women 30 years and under, of 61.5 percent in women 31 to 35 years of age, and of 53.6 percent in women 36 years of age and over (Fédération CECOS et al. 1982). In another French study on *in vitro* fertilization followed by embryo transfer, there was a significant decline in the pregnancy rate for women 39 years of age and over (Guichard et al. 1991).

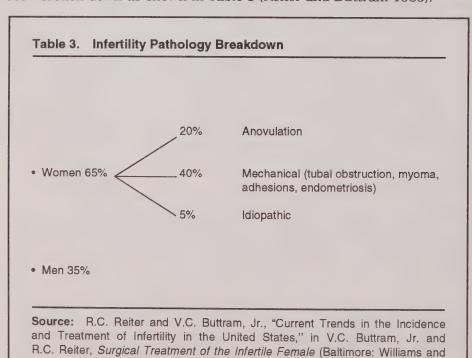
Wilkins, 1985).

Frequency of intercourse is also related directly to fertility (Table 2), and a decrease in this frequency with age further affects fertility for couples (Kinsey et al. 1953).

Age years)	Sexual intercourse (number of times per week)
6-20	3.7
1-25	3.0
6-30	2.6
31-35	2.3
36-40	2.0
11-46	1.7

When there are no pathologies present in either member of a couple, fertility depends on age and frequency of intercourse. Studies on fertility must therefore take into account these factors, which combine with all the other factors generated by the various pathologies and procedures that may affect the reproductive system.

The pathologies occurring in couples consulting for infertility have been broken down as shown in Table 3 (Reiter and Buttram 1985).



In 25 percent of the cases studied, both members of the couple showed anomalies that could explain the infertility. The investigation, treatment, and success rates vary with the types of pathology that occur.

Direct Procedures

Direct procedures resulting in infertility refer to surgery carried out on the male or female reproductive organs that leads directly to infertility.

Voluntary Sterilization

This section discusses voluntary sterilization techniques, such as tubal ligation and vasectomy, as well as the possible reversal of such procedures.

Voluntary sterilization is the most effective method of birth control, and it is very popular around the world (Rioux 1989; Hatcher et al. 1988). In 1990, there were an estimated 138 million married women around the world who had undergone voluntary sterilization (Table 4) (Church and Geller 1990, 4).

In 1984, sterilization was the most widely used contraceptive method in Canada (Balakrishnan et al. 1985). In Canada, approximately 57 000 vasectomies and 81 000 tubal ligations were performed in 1986 (Alderman and Gee 1989). From 1976 to 1986, there was a 26.7 percent decrease in tubal ligations and a 39.1 percent increase in vasectomies in Canada (Table 5). In Quebec, equal numbers of vasectomies and tubal ligations have been reported since 1986. In 1987, it was expected that these proportions would also occur in the other provinces of Canada in the years to come. Equal numbers of these procedures occurred in the United States in 1974 and in England in 1983 (ibid.).

In Canada, in 1979, one out of every two women was sterilized before the age of 41 years (Balakrishnan et al. 1985). Combining the figures for vasectomies and tubal ligations, in 1984, 83 percent of Canadian women in the 40 to 49 age group were in a state of voluntary infertility (ibid.). In Quebec, demographic data collected in 1987 indicated that the proportion of women sterilized by tubal ligation was 7 percent in the 25 to 29 age group and 21 percent in the 30 to 34 age group (Rochon 1989b, 29). In the 35 to 39 age group, a majority of women had had either a tubal ligation (46 percent) or a hysterectomy (7 percent), or had a vasectomized spouse (13 percent), which means that two-thirds of women in this age group either were sterilized or had a sterilized partner.

According to several authors, women who choose tubal ligation are usually married and have less education than women who use reversible contraceptive methods (Balakrishnan et al. 1985). According to another source, however, demands for sterilization occur later on in life in the case of more educated women because they marry and begin their maternity at a later age (Rochon 1989b).

Although a majority of women are satisfied with their sterilization, there is a percentage among them who experience regret. A Scandinavian researcher, in a literature review, estimated that from 1.3 to 12.7 percent of women were sorry in varying degrees that they had undergone sterilization (Kjer 1990).

In Quebec, a study conducted in Montreal in 1985, which surveyed 497 women aged 25 to 44 years (Marcil-Gratton 1988), reported that 13 percent of the women said they would like to have another child if they could (Table 6). According to the author, this percentage may be overestimated in view of the fact that the study was retrospective and may have awakened feelings of regret that had not manifested themselves before, thus biasing the women's response. The figures may be underestimated because some women may prefer to hide any regrets they may have from the investigator. However, 4 percent of the women interviewed had discussed the matter with their doctor and 1 percent of the 497 women surveyed had had the tubal ligation reversed (tubal re-anastomosis).

Table 4. Estimated Number of Married Women of Reproductive Age Voluntarily Sterilized for Contraceptive Purposes, 1990

Ago voluntarily cionizon to	% of	Number of MWRA
Region	MWRA	(in thousands)
DEVELOPING AREAS		
Africa	1	800
Asia & Pacific China Indian subcontinent Other Asia	30 18 10	63 200 41 800 7 200
Latin America & Caribbean	17	9 400
Near East & North Africa	2	700
All Developing Areas	. 18	123 100
DEVELOPED AREAS Europe		
East (includes USSR)	1	600
North (Scandinavia)	6	200
South West	2 7	300 2 100
United States	23	7 500
All Developed Areas	8	14 600
WORLD	16	137 700

MWRA = married women of reproductive age.

Source: C.A. Church and J.S. Geller, "Voluntary Female Sterilization: Number One and Growing," *Population Reports* [C] (10)(1990), 4.

a. 1976-1986, According to	
Table 5. Numbers of Vasectomies and Tubal Ligations Performed in Canada	Provincial Health Care Insurance Agencies

Vasectomy Tubal ligation Island Vasectomy Vasectomy Tubal ligation	t t									
Prince Edward Island Vasectomy		a t		1 1	1 1	721	870 979	1 100	1 137	1 292
and against	1 1		1 4	134 608	158	94	185 548	169	284	257
Nova Scotia Vasectomy 1 313 Tubal ligation 3 662	1 558 3 439	1 649 3 368	1 587 2 855	1 350 2 716	1 295 3 100	1 548 3 272	1 538 2 888	1 620 2 835	1 731 2 987	1 799 3 416
New Brunswick Vasectomy Tubal ligation	483 4 066	753 4 519	807	780	837 2 860	746 3 088	781	3 000	1 027 2 950	1 042
Quebec Vasectomy 7 771 Tubal ligation 27 395	9 991 31 806	13 777 32 368	14 161 27 477	15 317 26 705	13 000 23 517	15 541 24 636	15 134 23 187	17 189 22 880	17 981 22 041	19 491 [‡] 19 818 [‡]
Ontario Vasectomy Tubal ligation	13 565 36 095	15 359 34 196	13 797 29 936	12 296 28 940	10 934 29 740	12 086 28 283	12 760 27 943	14 912 29 579	15 802 28 737	17 774 27 975
Manitoba [†] Vasectomy 1 414 Tubal ligation 4 737	1 749 4 703	1 889 4 448	1 747	1 446 3 857	1 299	1 366 3 622	1 432 3 498	1 475	1 720	1 890 3 277

Province	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986
Saskatchewan											
Vasectorny	1 276	1 641	1 771	1 625	1 440	1 282	1 588	1 564	1 838	2 057	2 221
Tubal ligation	3 327	3 487	3 718	3 246	3 123	3 285	3 371	3 421	3 325	3 603	3 260
Alberta											
Vasectomy	2 568	3 265	3 555	3 139	2 951	2 373	3 008	3 691	3 995	4 799	5 337
Tubal ligation	6 030	8 625	8 723	8 266	7 982	9 051	9 169	10 075	9 332	9 889	10 003
British Columbia											
Vasectomy	5 070	5 011	5 201	4 511	4 182	3 737	4 565	4 522	5 313	5 502	6 114
Tubal ligation	10 857	9 424	9 975	8 977	6 646	7 236	8 731	8 559	8 885	8 939	8 870
Canada											
Vasectorny	19 412	37 263	43 954	41 374	39 896	34 915	41 263	42 474	48 570	52 040	57 217
Tubal ligation	56 008	101 645	101 315	89 330	83 850	83 051	85 662	83 902	84 841	84 020	81 023

Dashes indicate no or incomplete data.

Source: P.M. Alderman and E.M. Gee, "Sterilization: Canadian Choices," Canadian Medical Association Journal 140 (1989), 646. Reprinted by permission of the publisher.

Numbers in italics obtained from provincial medical association.

Estimates (see text [of original article] for details).

Table 6. Percent Distribution of Sterilized Women Aged 25 to 44, by Whether They Experienced Regret After the Procedure, According to Age at Sterilization

		Age at st	erilization	
Extent of regret	All (n = 495)	20-29 (n = 167)	30-34 (n = 222)	≥ 35 (n = 106)
Never regretted	74.9	64.1	79.7	82.1
Ever regretted	25.1	35.9	20.3	17.9
Did not discuss regret w/doctor	21.2	27.5	18.5	17.0
Did discuss	3.9	8.4	1.8	0.9
Did not request reversal	(2.7)	(5.4)	(1.3)	(0.9)
Did request	(1.2)	(3.0)	(0.5)	(0.0)
Would not have tried to have another child	7.3	8.9	6.8	5.7
Would have tried	12.7	20.4	8.6	9.4
Not sure	5.1	6.6	4.9	2.8
Total	100.0	100.0	100.0	100.0

Note: Percentages of women who "ever regretted," "discussed regret with a doctor," and "would have tried (to have another child)" differ significantly at $p \le 0.05$, according to age at sterilization.

Source: N. Marcil-Gratton, "Sterilization Regret Among Women in Metropolitan Montreal," *Family Planning Perspectives* 20 (1988), 224.

The authors of the *Population Reports* estimate that, around the world, approximately one to two women out of every thousand who have been sterilized would like to have their fertility restored (Henry et al. 1980). The corresponding rate for vasectomized men is estimated to be 2/1 000 (Liskin et al. 1983), but there have been very few studies on this subject (Leader 1989).

The women who are likely to request a tubal re-anastomosis are those who were sterilized young, who were in difficult socioeconomic circumstances, who were not particularly interested in working, who made their decision at the same time as another form of gynaecological or obstetrical procedure, such as giving birth or having an abortion, was being undergone, and whose conjugal life was rather complex (separation, divorce, new partner) (Gomel 1978; Henry et al. 1980; Vemer et al. 1986; Lennox et al.

1987; Marcil-Gratton 1988; Marcil-Gratton et al. 1988; Kjer 1990). The reason most commonly given by women for requesting tubal re-anastomosis is the desire to have a child with a new partner (Gomel 1978, 1980; Henry et al. 1980; Vemer et al 1986; Lennox et al. 1987; Marcil-Gratton 1988; Kjer 1990). Among men, a second marriage is also the main reason for requesting reversal of sterilization (Cos et al. 1983; Liskin et al. 1983).

This poses the question of the risks involved in microsurgical reversal of sterilization. In addition to the risks involved in anaesthesia and surgery, women who undergo such procedures are 2 to 10 times more likely to develop an ectopic pregnancy (Henry et al. 1980). The rate of spontaneous abortion following microsurgery is comparable to the rate among women who have not had such surgery (ibid.).

The main obstacles to tubal re-anastomosis are a lower fertility rate owing to increased age or to the overall health of the woman at the time of the request, as well as technical problems due to anatomical changes left by the earlier sterilization procedure (Henry et al. 1980).

The live birth rate following tubal re-anastomosis is approximately 60 percent (Table 7). The success rate in recent years may be explained by the use of atraumatic techniques for tissue manipulation and a more careful selection of candidates for the operation (Henry et al. 1980). The reversal of sterilization procedures that use a fallope ring or "clip" yield better results (Xue and Fa 1989), with a reported pregnancy success rate of up to 90 percent (Rock et al. 1987; Rioux 1989; Xue and Fa 1989).

The question of the maximum acceptable age for eligibility for tubal reanastomosis is frequently debated. A Dutch author reports a live birth rate following tubal re-anastomosis of 44 percent for women aged 40 to 44 years, compared to 66 percent for women of all other ages (Trimbos-Kemper 1990).

Vasovasostomy (re-anastomosis of the vas deferens following a vasectomy) is a relatively simple form of surgery, but it is not without complications (Cos et al. 1983; Hendry 1989). Reactions to anaesthesia and haematomas are the most frequent complications (Liskin et al. 1983). The success rate for vasovasostomy is measured in terms of the presence of viable sperm in the ejaculate and the pregnancy rate. According to various American studies reported by Cos et al. (1983), the viable sperm count following vasovasostomy is 74 to 100 percent, and the pregnancy rate varies from 39 to 78 percent (Table 8). Other success rates in various countries are reported in Table 9 (Liskin et al. 1983). The highest success rates were experienced when there was a short time between the vasectomy and the vasovasostomy (Cos et al. 1983). Liskin et al. and Cos et al., in their review of the literature, reported that a gap of less than two years between the two procedures makes it possible for the viable sperm count to rise as high as 91 percent, whereas it is only 35 percent when the period exceeds 10 years.

Hysterectomies

A hysterectomy is a surgical procedure that consists of removing the uterus. It may be accompanied by the excision of one or both of the adnexa (fallopian tubes and ovaries) and can be performed either abdominally or vaginally. Statistics, indications, and alternative therapies will be considered. The hysterectomy statistics given in this section are based on Statistics Canada data.

Statistics

In North America, hysterectomy is the second most frequent major surgical procedure (after Caesarian section) undergone by women (Allard and Rochette 1991). As Table 10 shows, the absolute number of hysterectomies and the hysterectomy rate in Canada have varied slightly over the past 20 years (January 1969 to March 1988). An increase in the hysterectomy rate was noted between 1969 and 1972. The maximum rate was reached in 1972, with 627 hysterectomies per 100 000 woman-years. Following this, a gradual decline occurred, and in 1988 the lowest level was reached — 457/100 000 woman-years. The decline in the hysterectomy rate from 1972 to 1988 was 27 percent (Figure 1).

The hysterectomy rates by Canadian province for the years 1969, 1973, 1977, 1981, 1985, and 1988 are listed in Table 11. The provincial trends are comparable to the national trends, except for increased rates in Newfoundland and Nova Scotia since 1985, as well as in New Brunswick and Saskatchewan in 1988. In 1988, Manitoba was the province with the lowest hysterectomy rate, that is, 373/100 000 woman-years, whereas the highest rate recorded was in Newfoundland, with 640/100 000 woman-years.

Table 12 gives the hysterectomy rates in Canada by age group. Women in the 35 to 54 age group have the highest hysterectomy rates, at 3 791/100 000 woman-years in 1973 and 2 295/100 000 woman-years in 1988. Within this range, women in the 35 to 44 age group have slightly higher rates than women in the 45 to 54 age group. The highest rates for these two age groups were recorded in 1973. From 1973 to 1988, a 43 percent decrease in these rates was noted in the 35 to 44 age group and a 23 percent decrease in the 45 to 54 age group. In the other age groups, trends vary, with decreases of 35 percent, 40 percent, and 32 percent in the 15 to 24, 25 to 34, and 55 to 64 age groups, respectively, from 1973 to 1988. The only age group in which there was an increase in the hysterectomy rate was those 65 years and older, for which the rate went from 280/100 000 in 1973 to 327/100 000 in 1988, an increase of 17 percent.

Thus the data show a decrease in hysterectomy rates over the past 20 years in Canada overall and in most provinces. The decrease has been in women under 65 years of age, with women 65 years of age or over showing an increase.

			Dates		% of	% of women experiencing outcome	eriencing	Ectopic/all
Author & date	Ref.	Country	of series	No. of cases	Live	Abortion	Ectopic pregnancy	pregnancies (%)
A. EARLY SERIES,	NO MAGN	ES, NO MAGNIFICATION, CONVENTIONAL TECHNIQUES	TIONAL TE	CHNIQU	ES			
Cordua 1952	55	Federal Rep. of Germany	1946-?	7	29ª	Z Z	N A	NA
Ekblad 1961	86	Sweden	Z Z	က	33ª	Z	NA	NA
Hellman 1956	122	ns	A N	က	33	0	0	0/4 (0) ^b
Milnor et al. 1950	197	NS	1940-	ന	29	Υ V	33	N
Milochevitch 1968	198	Yugoslavia	A N	2	0	Z	N A	NA
Mutch 1959	202	NS	1950- 1957	10	30ª	Υ V	Υ Z	Z Z
Peel 1964	229	Š	A N	ო	33ª	NA	NA	NA
Schmidt-Elmendorff 1948	265	Federal Rep. of Germany	N A	6	22ª	A A	₹ Z	N A
Traenckner 1953	308	Federal Rep. of Germany	1944- 1952	52	o _s	α	9	3/7 (43)
Total				92	16	υ	7	3/11 (27)

3/7 (43)	N A	1/6 (17)	A Z	Z Z	N A	0/1 (0)	0/4 (0)	5/24 (21)		8/34 (24)	0/8 (0) _h	₄ (0) 6/0	8/51 (16)
21	0	4	Z A	N A	¥ Z	0	0	79		15	0	0	6
0	₹ Z	0	₹ Z	₹ Z	V	0	13	49		0	0	Ŋ	-
29¢	29	22	20	20	38	ð	25	30	JES	49¢	50	42	48
41	ო	23	4	9	13	F	16	111	ECHNIQL	53	16	19	80
1972- 1976	1966- 1976	1953- 1973	1974-	1965- 1972	A A	1968- 1976	1957- 1972		MATIC T	1967- 1977	1973- 1975	1940-	
US	US	NS	Australia	NS	ž	US	Ä.		NIFICATION, ATRAU	US	NS	NS	
128	201	288	305	311	318	325	331		NO MAG	192	230	255	
Hondari et al. 1977	Musich et al. 1977	Siegler & Perez 1975	Thatcher 1978	Umezaki et al. 1974	Vartan 1973	Wheeless 1977	Williams 1973	Total	C. RECENT STUDIES, NO MAGNIFICATION, ATRAUMATIC TECHNIQUES	McCormick et al. 1979	Peterson et al. 1977	Rock et al. 1980	Total

			900		% of	% of women experiencing outcome	eriencing	Ectopic/all
Author & date	Ref.	Country	of series	No. of cases	Live	Abortion	Ectopic pregnancy	pregnancies (%)
D. RECENT STUDIE	S, MAGNI	UDIES, MAGNIFICATION, ATRAUMATIC TECHNIQUES	TIC TECH	NIQUES				
Ansari 1979	14, 16	NS	1973-	72	40	79	0	ر(0) لار)
Daniell 1979	89	NS	1976- 1978	24	20	A Z	4	₹
Diamond 1979	71	NS	1975- 1977	72	75	۷ ۷	0	N A
Diamond 1977	74	NS	1972- 1973	28	27		146	۷ Z
Gomel 1980	104	Canada	1971-	118	64	o	-	¥ Z
Hochuli & Gehring 1978	127	Federal Rep. of Germany	A A	12	25	25	17	2/8 (25) ^h
Jones & Rock 1978	158	SN	1977	12	75	N N	∞	A N
Lieberman & Anderson 1978	176	Ä N	1973-?	ო	33	33	0	0/2 (0) ^h
Nakamura 1980	206	Brazil	1978- 1980	ო	29	0	0	0/3 (0)
Novy 1980	212	US	1975- 1978	6	44	11	NA	_q (0) 9/0

Heaps 1977								
Paterson 1980	222	Australia	9-1979	20	40	. 9	4	2/25 (8) ^h
Rock et al. 1980	255	NS	1976- 1979	30	09	7	က	1/21 (5) ^h
Silber & Cohen 1980	292	ns	Z A	25	56	AN	4	٩Z
Vammen et al. 1979	317	NS	1962- 1977	17	59	8	Ø	1/14 (7) ^h
Williams 1977	328	NA NA	Y Y	25	72	NA	NA NA	٩Z
Wilson 1980	334	Australia	1974- 1975	14	39	വ	2	2/20 (10) ^h
Winston 1980	338	UK	Z A	126	28	NA A	2	V
Total				260	56	50	39	8/106 (8)

Australia

714

Owen & Pickett-

NA = not available.

* Please consult table source for complete bibliographic details.

Intrauterine pregnancies; outcome not reported.

Repeat live births reported. Insufficient number reported for derivation of meaningful totals. Possible ectopic pregnancy; lost to follow-up.

Includes spontaneous abortions, ectopic pregnancies, and molar pregnancies.

Live births plus intrauterine pregnancies continuing at time of report or when lost to follow-up. Based only on series reporting number of abortions or ectopic pregnancies.

No repeat live births reported; not known if any occurred. Rate of ectopic pregnancy therefore may be overestimated

Source: A. Henry et al., "Reversing Female Sterilization," Population Reports [C] (8)(1980), C100-C101

Pregnancy 8 46 43[‡] 40 64 39 53 54 50 57 71 Patency % 91 74* 633 88 90 96 83 90 64 83 83 Macro, 1-layer unstented Micro, 2-layer unstented Micro, 2-layer unstented Micro, 1-layer unstented Macro, 1-layer stented Macro, 1-layer stented Loupe, magnif. 1-layer Loupe magnif. 1-layer, Loupe magnif. 1-layer, Loupe magnif. 2-layer Loupe magnif. 1-layer "flap" unstented Macro, 1-layer Table 8. Six-Year Experience of Vasovasostomy in the United States **Technique** unstented unstented unstented unstented stented Time between (mean yr.) vas. and vasovas. 5.0 5.0 9.7 9 No. of cases 35 14 72 42 26 26 2 2 36 139 4 1978 1978 1978 1978 1979 Year 1980 1980 1980 1980 0861 1980 1981 Fallon, Miller, and Gerber⁶ Willscher and Novicki28 Lee and McLaughlin¹⁶ Middleton and Urry¹⁹ Fallon, Jacobo and Amelar and Dubin7 Kosterhalfen, and Middleton and Wagenknecht, Henderson¹⁷ Fitzpatrick²⁰ Schirren²¹ Bunge 18 Silber38 Series Ibid bidl

						oer ml.	* > 25 × 10 ⁶ sperm per ml.
	46	75	Micro, 2-layer unstented	5.4	87	1983	Cos et al.
	46	80	Micro, 2-layer unstented [¶]	5.6	47	1983	Requeda <i>et al.</i> ⁶¹
	65	:	Loupe magnif. 1-layer, stented	5.6	20	1982	Redman ²²
	78	82	Loupe magnif. telescoped unstented		27	1982	Hartig and Meyer ²³
	52	84	Loupe magnif. 1-layer, stented	:	20	1981	Urquhart-Hay ²⁵
	70	•	Loupe magnif. 1-layer, stented	6.1	10	1981	Shessel, Lynne, and Politano ²⁴
	75	1001	Micro, 2-layer unstented	8.7	Ф.	1981	Ibid
	29	177	Micro, 1-layer unstented	8.1	6	1981	Sharlip ²⁷
	43	06	Micro, 2-layer unstented	7.4	40	1981	Martin ⁵
	45	92	Loupe magnif. 1-layer, unstented	5.4	96	1981	Kessler and Freiha ¹¹
-	776	147	LICENSING CONTROL OF STREET STREET, ST				

< Ten years between vasectomy and vasovasectomy. Almost half without postoperative semen analysis.</p>
> 14 × 10⁶ sperm per ml.
< 20 × 10⁶ sperm × ml.

Seven cases done with macroscopic, single-layer technique.

Source: L.R. Cos et al., "Vasovasostomy: Current State of the Art," Journal of Urology 22 (1983), 572. Note: Please consult table source for complete bibliographic details.

Table 9. Pregnancy Rates Following Vasectomy Reversal, by Magnification Used, Selected Studies, 1967-1983

Author, date, & ref. no.	Place	No. of cases followed	Length of follow-up in years	Stent?	Magnifi- cation	Years between vasectomy & reversal (mean in parentheses)	% with sperm in ejaculate after reversal	Pregnancy rate (%)
WITHOUT MAGNIFICATION								
Denton et al. 1983 (126)	US	29		Yes		1-20 ^a (6)	₈ 96	99
	NS	35	<u>\</u>	a)	1	<20 (6)	83	40
	ž	13	≥1.5	Yes	I	0.6-10 (3.9)	100	85
	Canada	41	<u>^</u>	Yes	I	$0.5-15^{\circ}$ (5)	90	46
0	Sn (72	Z A Z	٥ ک	ł	NA N	94	39
	India	73		Yes	1	1-16	86	58
	Canada	7	-	Y Z	1	1-11 ^d	81 ^d	46°
	NS	21	<u>^</u>	Yes	1	1.7-12.1 (6.9)	67	29
		14		Yes	I	1-8.6 (4.8)	86 ^f	29 ^h
Schmidt 1975 (439)	ns	64	4		ļ	NA VA	78	31
WITH MAGNIFYING LOUPE								
Amelar & Dubin 1979 (29)	US	119	^2	°N,	*	NA	85	38
Bagshaw et al. 1980 (47)	숨	56	≥0.5	_ ;	* *	<10	91	25
Denton et al. 1983 (126)	NS	18		٥ ک	2.5×	1-20 ^a (6)	96	61
Fallon et al. 1981 (147)	NS	27/28 ^k	≥1.5	<u>8</u> ;	2.5×	AN	74	57
Fitzpatrick 1978 (158)	NS	14	0.5	°Z	AN	AN	100	64
Kessler & Freiha 1981 (255)	NS	83/71	ΥZ	<u>8</u>	4×	<20	92	45
Lee & MVSP 1980 (283)	South Korea	78		>	% ×		79	19
		222	√	Yes	4-6×	1-16	86	41
		300m			2-6× ^m		84 ^m	35 ^m

The state of the s									es. "
Ferreira 1981 (155)	Brazil	21	-	^o Z	Ϋ́Z	0-14	821	71	_
Gojaseni & Visuthikosol 1979	Thailand	ω	NA	°Z	16×	2-15	75	A A	
178)									
Kay et al. 1983 (251)	SN	25°	≥.25 ^p	ž	Ϋ́	1.25-15 (5)	96	Υ Z	
ee & McLoughlin 1980 (284)	Canada	26	∑i	%	ΥZ	$0.15-15^{\circ}$ (5)	96	54	
Martin 1981 (311)	NS	21		%	5-25×	1-19 (7.4)	06	43	_
Owen 1977 (361)	Australia	20	<u>t.</u>	Yes	۷ Z	6>	98	72	
Owen & Kapila 1981 (362)	Australia	400	22	%	25x	ΥZ	96	79	
	Canada	40		A A	ΥZ	1-119	81 ^d	46	
	NS	44	1.5	N A	16×	۲	82	16	
Silber 1979 (466)	NS	42	1.5	2°	16-25×	V	A Z	71	
Willscher & Novicki 1980 (540)	SN	12/10°	0.25-	°N	20× or	1.5-9	83	09	
			1.33		greater				
Rate for 54 cases (both with and without magnification) for which	h and without ma	agnification)	for which	k 27	patients had	27 patients had postoperative semen analysis;	emen analy	sis;	
semen analysis was performed	med.			pre	gnancy infor	pregnancy information available for 28 couples.	for 28 coup	oles.	
Stents used on patients 1968-71; no stents used 1972-75.	68-71; no stents	used 1972-	75.	83	patients had	83 patients had postoperative semen analysis;	emen analy	sis;	
For 87 cases; 67 followed u	followed up, 26 with and 41 without magnification	11 without m	nagnification.	pre	gnancy infor	pregnancy information available for 71 patients.	for 71 patie	ents.	_
Based on 47 cases, 40 with and 7 without magnification	and 7 without n	nagnification	٠	m Abc	ive two grou	Above two groups combined.			
Based on follow-up of 39 of 47 patients requesting reversal in an	f 47 patients requ	uesting reve	irsal in an	Spe	irm count >2	Sperm count >20 million per cubic cm.	bic cm.		
attempt to recover their fertility	illity.	•		° Pro	cedures don	Procedures done on outpatient basis under local	basis under	local	

Procedures done on outpatient basis under local anesthesia.

4 patients followed up for less than three months. Stent removed during procedure.

12 patients had postoperative sperm analysis; Sperm present in "significant numbers."

pregnancy rate determined from 10 cases eligible wife fertile).

Note: Please consult table source for complete bibliographic details.

Various techniques used, both with and without stent. Nylon stent used only if reversal technically difficult.

8 patients followed up for less than one year. Absorbable splint of catgut left in place. Sperm count >10 million per cubic cm.

Source: L. Liskin, J.M. Pile, and W.F. Quillin, "Vasectomy — Safe and Simple," Population Reports [D] (4)(1983), D-79.

Table 10. Number and Rates of Hysterectomies, Canada, 1969-1988

Year	Hysterectomies* (n)	Rates** per 100 000
1969	49 495	472
1970	58 549	550
1971	66 925	622
1972	68 415	627
1973	67 710	614
1974	67 137	599
1975	65 153	572
1976	60 264	523
1977	62 871	539
1978	61 830	524
1979***	60 234	502
1980	60 309	497
1981	60 367	491
1982	61 509	494
1983	60 845	484
1984	60 790	478
1985	61 449	482
1986	61 447	478
1987	62 338	480
1988	60 177	457

^{*} Number of hysterectomies according to Statistics Canada data.

Table 11. Hysterectomy Rates,* Canadian Provinces, 1969, 1973, 1977, 1981, 1985, 1988

Year	Nfld.	P.E.I.	N.S.	N.B.	Que.	Ont.	Man.	Sask.	Alta.	B.C.
1969	293	328	539	521	442	460	333	521	611	556
1973	422	482	749	675	683	560	446	569	719	618
1977	543	524	705	621	585	481	418	368	581	623
1981	537	451	554	584	559	462	384	353	428	512
1985	629	479	572	559	498	459	405	383	501	503
1988	640	422	587	589	437	449	373	413	479	460

^{*} Hysterectomy rates per 100 000 woman-years based on the absolute number of hysterectomies and Statistics Canada's estimates of female population by province.

^{**} Rates computed on the basis of Statistics Canada's annual estimate of Canada's female population (see Table 13).

^{***} Change from calendar year to fiscal year, representing 15 months.

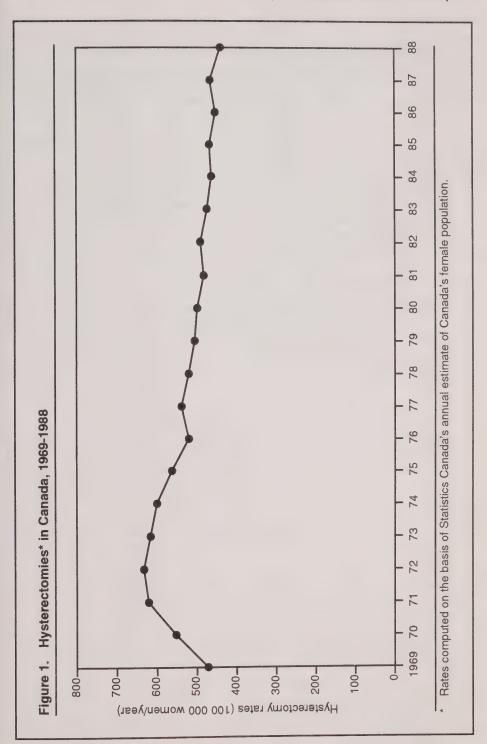


Table 12. Hysterectomy Rates* by Age Group, Canada, 1969, 1973, 1977, 1981, 1985, 1988

Year	15-24	25-34	35-44	45-54	55-64	65+
1969	20	511	1 593	1 377	491	287
1973	43	787	2 169	1 622	570	280
1977	49	738	1 759	1 311	528	300
1981	41	648	1 545	1 132	411	287
1985	34	563	1 401	1 105	385	304
1988	28	470	1 231	1 064	387	327

^{*} Hysterectomy rates per 100 000 woman-years based on the absolute number of hysterectomies and Statistics Canada's estimates of female population by age group.

Table 13. Female Population, Canada, 1969-1988

Year	Number* (000s)
1969	10 470.3
1970	10 647.6
1971	10 753.7
1972	10 908.6
1973	11 033.2
1974	11 211.4
1975	11 390.8
1976	11 526.1
1977	11 667.0
1978	11 788.8
1979	11 993.1
1980	12 147.7
1981	12 293.3
1982	12 442.0
1983	12 571.1
1984	12 707.3
1985	12 739.4
1986	12 850.4
1987	12 997.4
1988	13 153.5

^{*} Annual estimate of Canada's female population from Statistics Canada records.

The hysterectomy figures given in Tables 10, 11, and 12 are underestimates. They do not include women who have already had hysterectomies, and the computations use the annual estimate for the

general population as a denominator. This underestimate is likely to be most significant for older women. However, the rates reported follow similar trends to those computed by Allard and Rochette (1991) for Quebec from 1981 to 1988 using life tables. This method, which ideally should be applied to cohorts, makes it possible to provide more accurate estimates; it does, however, require information and computations that go beyond the scope of this report.

Indications

According to Allard and Rochette (1991), the main indications for hysterectomy in Quebec are uterine leiomyomas, menstrual problems, and endometriosis. Uterine prolapse is the main reason for hysterectomies in women over 50 years of age. Hysterectomies for genital cancer account for 7.3 percent of the total number. According to the authors, there was a decline in all age groups from 1981 to 1988 in the rate of hysterectomies performed as a result of endometriosis, probably because of the introduction of alternative medical treatments.

Noralou Roos, a Manitoba author, reports that menstrual disorders are the main indication for hysterectomy (Roos 1984). It is important to note that, clinically speaking, uterine leiomyomas (the main cause of hysterectomies in Quebec) frequently cause menstrual problems.

In a study carried out in Maine in the United States, the main indications for hysterectomy from 1988 to 1990 were uterine leiomyomas and benign tumours, endometriosis, and uterine prolapse (B.A. Miller,

personal communication).

In Quebec, we note that the practice of performing a bilateral ovariectomy in conjunction with a hysterectomy dropped from 35 to 30 percent from 1981 to 1988 (Allard and Rochette 1991). This slight decline appears only in women 50 years of age and under. In 1988, the proportion of Quebec women having undergone surgical castration was 9.2 percent for women in the 30 to 34 age group, 10.5 percent for women in the 35 to 39 age group, 19.4 percent for women in the 40 to 44 age group, and 50 percent for women in the 45 to 49 age group. Moreover, the proportion of hysterectomies performed vaginally was 16 percent in Quebec, compared to 25 percent in the United States (ibid.).

Alternative Therapies

Alternatives to hysterectomy — treatments that make it possible to avoid or delay a hysterectomy — are many. Whether the therapies involve the use of drugs or procedures like curettage or hysteroscopy, these approaches have a therapeutic effect that varies, depending on the underlying pathology, the age of the woman, and the length of treatment (Mailloux 1992). For example, medical treatment of uterine leiomyoma with LH-RH agonists is an alternative form of therapy for women who wish to remain fertile. Its effectiveness has been demonstrated (Maheux et al. 1985; Matta et al. 1989). The side-effects of this form of therapy (osteoporosis, changes in the lipid balance), as well as a recurrence of the problem after the end of treatment, call for caution (Matta et al. 1989).

The recently developed surgical hysteroscopy is another example of an alternative therapy for recurring and persistent dysfunctional bleeding even after curettage or medical treatment (Laberge 1991). Hysteroscopy treatment of submucosa uterine myomas and polyps now makes it possible to delay and sometimes prevent the need for hysterectomy in some cases. It also makes it possible for the woman to remain fertile. The endomectomy or ablation of the endometrium is a new surgical procedure that uses hysteroscopy to perform a total resection of the endometrium, thus treating dysfunctional bleeding. The endomectomy, which is a much less invasive procedure than hysterectomy, must nevertheless be performed only when the woman no longer wishes to become pregnant, because it theoretically makes the woman infertile. A healing rate of up to 90 percent is reported in women with menometrorrhagia that resisted medical treatment. In the short term, this form of treatment appears promising, but it is too early to determine its long-term effectiveness (ibid.).

Because the effectiveness of these alternative therapies is not covered by this report, we shall not discuss them in further detail. However, it is worth noting that we could not find any papers on the percentage of hysterectomies avoided through the use of these alternative therapies.

Our review of the literature did not go into detail about surgical procedures for men that have a direct impact on fertility (orchidectomy, penectomy). Such procedures, which are relatively rare, are indicated primarily in cases of testicular cancer treatment, torsion of the testicle, or sex change operations (Smith 1975).

Procedures Likely to Indirectly Cause Infertility

Diagnostic and therapeutic tests and surgery either on the male or female reproductive organs, or on other organs, may eventually give rise to infertility. Infertility thus can be caused by the procedure or complications related to the procedure.

Prenatal Tests

Prenatal screening techniques make it possible to detect genetic diseases and congenital fetal malformations. We will examine amniocentesis, chorionic villus sampling (CVS), and cordocentesis and their possible impact on fertility.

Amniocentesis

Doctors began to use amniocentesis in the 1950s (Nolan et al. 1981). In 1991, the Canadian College of Medical Geneticists (CCMG) and the Society of Obstetricians and Gynaecologists of Canada (SOGC) published its recommendations for prenatal diagnostics in Canada (CCMG and SOGC 1991). According to this paper, amniocentesis is recommended in the following situations:

- advanced age of mother at time of delivery (over 35 years);
- history of stillborn child or of child born living but with a chromosomal abnormality;
- chromosome translocation in the family;
- history of specific congenital abnormalities (neural tube defects);
 and
- the identification of other biochemical or molecular genetic diseases that may be obtained through analysis of the amniocytes or amniotic fluid.

An amniocentesis is performed after the fourteenth week of gestation (Porreco et al. 1982; Rhoads et al. 1989; CCMG and SOGC 1991; Johnson 1991; Lippman et al. 1992). First, an ultrasound determines the age of the fetus, the location of the placenta, cardiac activity, and the number of embryos (CCMG and SOGC 1991). A small sample of amniotic fluid is then removed by means of a needle inserted through the abdominal wall and into the cavity of the uterus (ibid.; Johnson 1991; Lippman et al. 1992). Women experience some uterine cramps, but these are not usually traumatic (CCMG and SOGC 1991).

The risk of miscarriage following amniocentesis has been studied in depth, and the percentage has been found to be in the order of 0.5 (Porreco et al. 1982; Daker and Bobrow 1989; O'Connor et al. 1989; CCMG and SOGC 1991; Johnson 1991).

Early amniocentesis (prior to 15 weeks) appears to be a possibility, but clinical studies of this method are only just beginning (Nevin et al. 1990). The risk of miscarriage with early amniocentesis is estimated at between 1.0 and 4.7 percent (ibid.; CCMG and SOGC 1991).

With the exception of miscarriage, no study has been able to draw a link between amniocentesis and infertility.

Chorionic Villus Sampling

Chorionic villus sampling is a prenatal screening procedure performed under ultrasound during the first trimester of pregnancy, that is, between the ninth and twelfth weeks of pregnancy (CCMG and SOGC 1991). It consists of taking a biopsy of the chorion, either transcervically or transabdominally. Chorionic villus sampling can be used to analyze chromosomes and DNA, and it can also be used for metabolic tests.

The transabdominal technique is used for approximately 20 percent of CVSs carried out around the world (Johnson 1991). Choosing between the transabdominal and transcervical techniques is based on the experience of the surgeon (CCMG and SOGC 1991; Johnson 1991), the woman (CCMG and SOGC 1991), and the location of the chorion (Johnson 1991). Neither form is usually traumatic (CCMG and SOGC 1991).

The reason for choosing CVS over amniocentesis is that it makes it possible to obtain results early during pregnancy (CCMG and SOGC 1991; Johnson 1991). This means that if a significant abnormality is present, an

early abortion would be safer and could be less painful emotionally. However, the problem with the procedure is that it does not detect neural tube problems, which means that another ultrasound is required between the sixteenth and twentieth weeks to complete the investigation, or a maternal serum alpha-fetoprotein analysis must be done. In addition, if there is a chorionic mosaicism (a difference between the chromosomes in the chorion and fetal tissues), then a complementary amniocentesis is needed (ibid.).

In 1989, Rhoads et al. (1989) conducted a random study comparing the safety of CVS with that of amniocentesis. The incidence of miscarriages was 7.2 percent in the CVS group (n = 2.278) and 5.7 percent in the amniocentesis group (n = 671). It should be mentioned that these rates include all miscarriages that occurred in the first weeks of pregnancy, that is, miscarriages not linked to the procedure and those that might possibly follow treatment. When adjusted statistically, the difference between the percentages in the two groups was only 0.08 (IC 80 percent = -0.6 at 2.2percent). The position of the placenta, the number of samples taken, the quality of tissue collected, and the occurrence of vaginal bleeding prior to the procedure determine the miscarriage risk factors following CVS. The authors estimated that the proportion of women who had an abortion induced for sex selection reasons was less than 1 percent, although institutional policies did not allow this indication. Although possible, no cases of septicaemia were noted in the 2 278 women who underwent CVS. Of the 89 women who had spontaneous abortions, 12 had signs of pelvic inflammatory disease (PID).* The diagnostic reliability of CVS was demonstrated in this study. Only 0.8 percent of women had to have an amniocentesis to clarify the diagnosis obtained by CVS. These results are comparable to those reported in other studies (ibid.).

The Canadian multicentre randomized trial carried out in 1984 yielded similar results (Lippman et al. 1992). The rate of spontaneous abortions was 7.6 percent in the CVS group (n = 1 191) and 7.1 percent in the amniocentesis group (n = 1 200), a difference of 0.5 percent, which is not statistically significant. The diagnostic reliability of CVS in this study proved to be slightly lower than that of amniocentesis, and significantly so (2.3 percent error vs. 0.1 percent error, p < 0.0001). Moreover, although the study was not designed to measure the sensitivity and specificity of the two techniques, the authors were able to determine that the number of false-negatives (failure to diagnose an actual abnormality) was very low in both groups. The number of false-positives (diagnosis of an abnormality that does not actually exist) was slightly higher, particularly in the CVS group.

The risk of spontaneous abortion post-CVS seems slightly higher - 0.5 to 0.8 percent - than that post-amniocentesis. The difference is

^{*} The link between PID and infertility will be examined in those sections dealing with diagnostic tests and gynaecological procedures.

minimal and risk factors must be taken into account before choosing one or the other technique. As well, with the exception of spontaneous abortion, no study has been able to establish a link between CVS and infertility.

Cordocentesis

Cordocentesis consists of sampling the umbilical blood of the fetus transabdominally beginning as early as the twelfth week of pregnancy to term, for diagnostic purposes (CCMG and SOGC 1991). The two main indications for cordocentesis are a search for the fetal karyotype and the diagnosis of iso-immunization (Johnson 1991). Complications with this technique are rare. Death *in utero* occurs in 1 to 2 percent of cases (CCMG and SOGC 1991; Johnson 1991), particularly in fetuses with numerous or serious malformations and in those affected by retarded development (intrauterine growth retardation) (CCMG and SOGC 1991).

In summary, the spontaneous abortion rate following amniocentesis is 0.5 percent and that of CVS is 0.5 to 0.8 times higher. Death *in utero* following cordocentesis occurs in 1 to 2 percent of cases, particularly in fetuses that are already affected. With the exception of these complications, no other study has established a link between amniocentesis, CVS, or cordocentesis and infertility.

Diagnostic Tests

The purpose of the diagnostic tests described in this section is to identify the etiology of female or male reproductive system problems. The diagnostic tests performed on women that are considered here are hysterosalpingography, endometrial biopsy, hysteroscopy, and laparoscopy. Diagnostic tests performed on men are vasography and testicular biopsy. Tubal insufflation is not discussed in this report, because it has disappeared from the medical diagnostics arsenal.

Hysterosalpingography

The purpose of hysterosalpingography is to identify abnormalities in the uterus and the fallopian tubes. In infertility assessments, hysterosalpingography makes it possible to identify uterine abnormalities in 10 percent of women (Pittaway et al. 1983).

In this review of the literature, no study could be found that offered a direct analysis of the impact of hysterosalpingography on future fertility. Rather, the articles surveyed discussed hysterosalpingography complications, especially infections.

In the United States, Stumpf and March (1980) reviewed the literature and reported a post-hysterosalpingography infection risk that varied from 0.3 to 1.3 percent. In their own study, Stumpf and March found a higher incidence of PID, 3.1 percent (14 cases out of 448 hysterosalpingographies). This discrepancy stems from the fact that the criteria used to diagnose PID varied from one study to another. Some used simple abdominal pain as a

criterion (ibid.), which resulted in overestimating the rate of PID. Others deemed clinical criteria insufficient to diagnose PID (Jacobson and Weström 1969; Sellors 1991).

In order to demonstrate how difficult it was to diagnose acute PID, Jacobson and Weström performed laparoscopies on 905 other women who had had no hysterosalpingography and who had been clinically diagnosed as having acute PID based on the usual criteria such as sharp abdominal pain, leukorrhoea, fever, menstrual irregularity, and painful pelvic examinations. Preoperative PID was confirmed in only 65 percent of cases; in 23 percent, the laparoscopy revealed normal genital organs, and in 12 percent another pathology was identified.

Weström (1975) was one of the first researchers to underline the cause-and-effect relationship between PID and infertility. He estimated the risk of infertility following an initial occurrence of PID at 12.8 percent. Hysterosalpingography may have a negative impact on fertility in certain cases, but that impact is difficult to quantify on the basis of the studies analyzed above.

In order to minimize the risk of infection following hysterosalpingography, it is recommended that vaginal specimens be taken beforehand to check for STDs (Møller et al. 1984). Pittaway et al. (1983) also recommend a prophylactic antibiotic therapy (Doxycycline) for all women suspected of or reporting prior PID, or for women for whom the risk of PID following hysterosalpingography is high. The prophylactic antibiotic therapy cannot, according to Siegler, prevent all infections (Siegler 1983). Where a tubal dropsy is demonstrated during hysterosalpingography, immediate antibiotic treatment is necessary (Pittaway et al. 1983). The patients at highest risk of developing a febrile reaction are those with distal obstructive abnormalities in the fallopian tubes at the time of examination, whereas those with normal fallopian tubes are less at risk (Siegler 1983).

Endometrial Biopsy

Endometrial biopsy is frequently used in assessing fertility. It consists of taking a sample of the endometrium in the premenstrual phase to confirm that ovulation is taking place and to eliminate the possibility of an inadequate luteal phase. The endometrial biopsy may also be used to identify other endometrial pathologies such as chronic endometritis or endometrial hyperplasia.

According to the studies analyzed, the risk of removing the conceptus at the time of the biopsy ranges from 0.6 to 3.6 percent (Wentz et al. 1986; Wild et al. 1986; Kaminski and Lyon 1990). In their literature review, Wentz et al. (1986) report a risk of conceptus removal ranging from 1.3 to 6.3 percent, except for one study, in which the risk was identified as 20 percent (Table 14).

The risk of miscarriage for women undergoing an endometrial biopsy in early pregnancy ranges from 17 to 22 percent (Wentz et al. 1986; Wild et al. 1986), which compares to the risk reported for infertile women who had not undergone an endometrial biopsy (Wild et al. 1986).

Because the examination is performed following ovulation (and hence after conception may have taken place), the use of a barrier-type contraceptive during the menstrual cycle in which the endometrial biopsy is to be performed would prevent this type of incident (Wild et al. 1986; Kaminski and Lyon 1990).

No data on the risk of infection (endometritis) following endometrial biopsy were found in the literature.

Table 14. Spontaneous Abortions Following Endometrial Biopsy in the Cycle of Conception

	Total no.	Total in	First- trimester		Delivered	Total preg- nancy wastage
Author	biopsies	(%)	abortions	Ectopic	(%)	(%)
Wilson et al., 1966 ¹¹	NS	18			18	0
Buxton and Olson, 1969 ⁸	1 700	22 (1.3)			20 (91)	2 (9)
Karow et al., 1971 ⁹	1 000	28 (2.8)	2	1	22 (79)	6 (21)
Arronet et al. ¹²	NS	23	7		14 (61)	7 (30)
Rosenfeld and Garcia, 1975 ¹³	NS	18	1		15 (83)	1 (6)
Wentz, 1980 ³	210	10 (4.8)	0	1	9 (90)	1 (10)
Jacobson and Marshall, 1980 ¹⁴	35	7 (20.0)	1		6 (86)	1 (14)
Sulewski, 1980 ¹⁵	288	18 (6.3)	4		14 (78)	4 (22)
Present series	1500	54 (3.6)	9	2	40 (74)	11 (20)

NS, not stated.

Note: Please consult table source for complete bibliographic details.

Source: A.C. Wentz et al., "Cycle of Conception Endometrial Biopsy," *Fertility and Sterility* 46 (1986), 198. Reproduced with permission of the publisher, The American Fertility Society.

Hysteroscopy

The hysteroscopy consists of performing an endoscopy to view the interior of the uterus in order to perform a diagnosis or therapy (for infertility, uterine malformations, polyps, adhesions, uterine leiomyomas, etc.) (Taylor and Goswany 1989). Although hysteroscopy has been performed for over a hundred years, it has received much more attention in recent years (Cohen and Dmowski 1973; Laberge 1991). The technique is considered relatively safe and simple, and it can even be carried out under local anaesthetic (Cohen and Dmowski 1973).

In the literature, there is virtually no documentation concerning complications of hysteroscopy that could affect future fertility. A hysteroscopy may exacerbate a latent pelvic inflammation, and that is why patient history and a pelvic examination are important prior to the procedure (Siegler 1984). Salpingitis and peritonitis following hysteroscopy generally respond favourably to antibiotic treatment (ibid.). Uterine perforation is a possible complication (Valle 1983; Gomel et al. 1986), but we have found in the literature no quantitative data concerning its occurrence or its impact on future fertility.

Laparoscopy

Laparoscopy is a technique that makes it possible to view the contents of the abdominal cavity. Intra-abdominal pathologies can be identified and treated, and, in some cases, more invasive surgical procedures such as laparotomy can be avoided.

In gynaecology, indications for laparoscopy are many. The evaluation and treatment of female infertility are among the most frequent of these (Borten 1986). Trimbos-Kemper et al. (1982) report that, among infertile women who showed no initial risk factors for fallopian tube problems, laparoscopy identified abnormalities of the fallopian tubes in 37 percent of them (Table 15). A laparoscopy also makes it possible to determine the causes of acute and chronic abdominal pain; it allows diagnosis of and, where applicable, treatment of ectopic pregnancies and pelvic masses; lastly, it is used to perform surgical sterilizations (Mattingly and Thompson 1985). There is a growing interest in the technique for other special surgical procedures (Borten 1986), such as treatment of cholelithiasis, cholecystectomy, et cetera.

As listed in Table 16, the main complications of laparoscopy are pneumoperitoneum complications, bleeding, emergency laparotomies, various perforations, et cetera (Phillips 1977). These complications were computed on the basis of 145 000 laparoscopies reported by the American Association of Gynecological Laparoscopists (ibid.), and Loffer and Pent (1975). The mortality rate for diagnostic laparoscopy is estimated at 0.11/1 000 (Phillips 1977).

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No. of potential risk factors per patient	Total	With tubal abnormalities	%
0 (negative)	367	134	37
1	247	166	67
2	109	87	80
3	53	47	89
4 or more	44	40	91
Total	820	474	58

Source: T. Trimbos-Kemper, B. Trimbos, and E. van Hall, "Etiological Factors in Tubal Infertility," *Fertility and Sterility* 37 (1982), 385. Reproduced with permission of the publisher, The American Fertility Society.

Table 16. Incidence of Complications of Laparoscopy

	Rate/1 000 cases
Pneumoperitoneum complications	7.4
Bleeding	6.4
Laparotomies necessary	5.6
Perforation injuries	2.7
Pregnancy after sterilization	2.5
Electrical complications	2.2
Infection	1.4
Bowel burns	0.5
Cardiac arrest	0.3

Source: J.M. Phillips, "Complications in Laparoscopy," *International Journal of Gynaecology and Obstetrics* 15 (1977), 158.

Infectious complications following laparoscopy are rare (Loffer and Pent 1975; Borten 1986). In over 100 000 laparoscopies, the incidence of infections of all kinds was reported as 1.4/1 000 (Loffer and Pent 1975; Phillips 1977). Infection may have been due to, among other things, instrument contamination or micro-organisms already present in the abdomen (e.g., latent salpingitis) (Loffer and Pent 1975; Borten 1986).

Loffer and Pent (1975) report that the infections that occur following a laparoscopy are frequently limited to skin infections and are therefore without consequence and require no treatment. In his literature review, Borten (1986) reports rates of 0.8 to 1.3 percent for infections at the incision site following voluntary sterilizations.

The incidence of peritonitis following laparoscopy is difficult to establish, because other procedures are often used at the same time (bimanual examination, insertion of intrauterine manipulator, curettage, test of tubal permeability) (Borten 1986). For example, the risk of peritonitis when a laparoscopy is performed at the same time as a dilatation and curettage (D&C) is 3 to 5 per 1 000 procedures. The risk of peritonitis when a laparoscopy is accompanied by a tubal permeability test is approximately the same as for a hysterosalpingography (ibid.). When a gastrointestinal lesion occurs during laparoscopy (perforation or intestinal burns), peritonitis may follow (ibid.; Levanthal 1986). This type of peritonitis occurs in 0.5 of every 1 000 procedures performed (Levanthal 1986).

When PID is present or suspected at the time of the laparoscopy, it is recommended that injections not be performed transcervically, in order to decrease the risk of pelvic inflammatory infection (Borten 1986). According to Loffer and Pent (1975), a prophylactic antibiotic therapy is not necessary before a laparoscopy.

None of the scientific papers surveyed discusses the impact of

infectious complications of laparoscopy on fertility.

The risk of uterine perforation during laparoscopy is approximately 30.4 per 1 000 procedures (White et al. 1977). The risk is higher for women over 34 years of age, women who have given birth frequently, and women who are obese (Borten 1986). When the perforation haemorrhages, the haemorrhage is generally easy to control by electrocoagulation (Loffer and Pent 1975; White et al. 1977; Borten 1986).

No data were found concerning the impact of uterine perforation on fertility.

The laparoscopist's experience is crucial in minimizing complications. These occur primarily when the person performing the operation has done fewer than 100 laparoscopies (Phillips 1977).

In summary, there are very few data on the impact of laparoscopy on fertility; however, the risk of infection following use of this technique is slight and the risk of infertility rare.

Vasography

Vasography is a radiographic technique used on men to examine the vas deferens and to identify any obstructions. It is necessary prior to any corrective microsurgery on one or the other vas deferens (Bertram et al. 1985). Vasography is also used in evaluating the seminal vesicles and to investigate perineal pain, haemospermia, and, more recently, prostate cancer (ibid.).

Occlusions of the excretory organs represent 7.4 percent of cases of male infertility (Sherins and Howards 1986). According to Payne et al. (1985), vasography demonstrated occlusion in 10 percent of azoospermic men.

Vasography may be accompanied by complications. In 509 azoospermic men, vasography led to obstruction of the vas deferens in 3 percent of cases (Wagenknecht et al. 1982). These vasographies had been performed using a conventional contrast medium. The authors concluded that the use of this product was harmful and recommended the use of a saline solution. Using a needle to puncture the vas deferens appeared to them less traumatic than cannulation (ibid.).

A comparison of the sperm analyses done prior to 154 vasographies and those done three months later to identify any possible modifications in the sperm count showed identical results in 92 percent of cases. No information is available on the 8 percent of men whose semen analysis still showed differences after three months.

To reduce the risk of complications, Ford et al. (1982) recommended beginning with a unilateral vasography. If an obstruction is identified, a contralateral vasographic examination can then be performed with a view to diagnosing the need for corrective surgery. If, on the other hand, no obstruction is diagnosed, the contralateral vasography will not be necessary because one permeable vas deferens is sufficient for sperm transport (ibid.).

Because of the success of microsurgery methods, many researchers have concluded that the use of vasography is justified even though complications have been reported (Bertram et al. 1985; Payne et al. 1985; Sherins and Howards 1986).

Testicular Biopsy

Testicular biopsies have been used for over 50 years to investigate male infertility (Gordon et al. 1965; Cohen et al. 1984; Coburn et al. 1987). A testicular biopsy consists of sampling testicular tissue for histological analysis under local anaesthetic. In infertile men with normal testicular volume, such a biopsy helps to differentiate testicular deficiency from obstructions (Cohen et al. 1984; Sherins and Howards 1986; Jarow et al. 1989). It has become increasingly important to diagnose obstructive pathologies, what with the growing success of microsurgical techniques to correct this cause of infertility (Cohen et al. 1984).

Data reported by Gordon et al. in 1965 suggest that testicular biopsies may lead to a temporary decrease in sperm production. They note that a decrease in the sperm count has been noted only for a short time following biopsy. A more recent study did not note this effect (Coburn et al. 1987).

Gordon et al. (1965) raised the hypothesis that an immunological reaction could explain the decline in the sperm count following biopsy. However, Ansbacher and Gangai (1975), a few years later, did not find any circulating antibodies, even up to 14 days following the biopsy.

Infection from this technique has been observed in only a few isolated cases (Gordon et al. 1965; Cohen et al. 1984; Coburn et al. 1987).

Obstetrical Procedures

The Caesarian is the focal point of this section on obstetrical procedures. Other procedures (the use of fetal vacuum and other instruments) will be discussed in the analysis of the impact of Caesarians on fertility.

In the 1940s, the Caesarian was infrequently used, primarily when labour was difficult. At that time, the incidence of births by Caesarian section in England was estimated at 3 percent. As surgical techniques and anaesthetics improved, the Caesarian became less distressing and physically less traumatic, which led to its more frequent use (Hall et al. 1989).

Figure 2 and Table 17 present international comparisons of Caesarian rates (Ontario, Cesarean Birth Planning Committee 1991). Percentages in Canada and by province are given in Table 18. In Canada in 1969, 1 woman in 20 gave birth by Caesarian section; in 1985, almost one in five births were Caesarians (ibid.).

In light of the increase in the number of Caesarians in recent years, there is concern about the impact on fertility.

Zdeb et al. reported that in New York in 1975, women who had undergone a Caesarian for their first delivery had 11 percent fewer children in the five years following the operation than those who had given birth normally (Zdeb et al. 1984). This comparative study (two cohorts with 5 533 women in each) was based on national records. However, it would appear that problems were encountered in doing a thorough follow-up (Hall et al. 1989). Another study conducted in Sweden noted the same phenomenon (13 percent fewer children for women who had had a Caesarian), but the data were never published (Hemminki et al. 1985) and are therefore unavailable for analysis.

In 1985, Hemminki et al. reported in an American publication that the rate of spontaneous abortion following a Caesarian was identical to that for vaginal delivery. They also noted that the average interval between the first and second delivery was longer after Caesarians, at 4.3 years compared to 3.3 years for vaginal delivery. Lastly, they found that the voluntary sterilization rate was higher for women who had had a Caesarian. The live birth rate was 11 percent following a Caesarian and 12 percent following vaginal delivery. According to Hall et al. (1989), who reviewed the Hemminki et al. (1985) study, that difference is not significant. It is worthy of note that the data analyzed by Hemminki et al. were collected by means of questionnaires sent directly to women, and recall bias may have been introduced (Hall et al. 1989). Moreover, Hall et al. noted differences between cases of Caesarians and controls (vaginal deliveries) who had not been monitored, which may have affected the validity of the results.

In England, Hall et al. (1989) studied a population of 22 948 primiparous women and analyzed certain fertility criteria following vaginal delivery with forceps (n = 6507) or without instruments (n = 14448), and after a Caesarian (n = 1993). The authors reported that, following a Caesarian or a vaginal delivery with instruments, the percentage of births

was lower and the proportion of spontaneous abortions higher than following vaginal delivery without instruments (Tables 19 and 20) (ibid.). They also found that the rate of voluntary sterilization was slightly higher in these two groups (Caesarian and vaginal delivery with instruments).

Caesarian or vaginal births with instruments could therefore be associated with relative infertility (Hall et al. 1989). The physical trauma experienced during such deliveries could discourage some women from repeating the childbirth experience. The personal characteristics of these women could also explain the subsequent decrease in fertility (ibid.).

It is also important to study the infectious complications of Caesarians in order to analyze the impact of this operation on subsequent fertility. According to Valenzuela (1984), the occurrence of post-Caesarian endometritis did not significantly affect the number of pregnancies following Caesarian delivery. The author concluded that post-Caesarian endometritis played a minimal role in the impact of Caesarians on subsequent fertility.

In reviewing post-Caesarian febrile morbidity, Hurry et al. (1984) reported that puerperal endometritis and pelvic cellulitis did not diminish subsequent fertility. However, the presence of a post-Caesarian pelvic abscess decreased the subsequent pregnancy rate by one-third.

Data found in certain studies lead us to believe that Caesarian deliveries have an impact on fertility. However, analysis of these scientific papers reveals biases that put in doubt the validity of their conclusions. The physical trauma experienced during a difficult delivery could discourage some women from repeating the childbirth experience and incite them to opt for a permanent method of contraception. Infectious complications of Caesarians do not seem to have an impact on fertility.

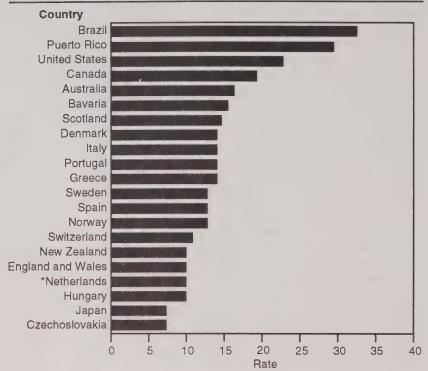
Gynaecological Procedures

Gynaecological procedures are operations on female genital organs. We have placed the subsection on induced abortion here, because it relates to female fertility. This section thus will discuss the use of the intrauterine device (IUD), cervical procedures, and induced abortion. Information about curettage will be found in the subsection on induced abortion.

The Intrauterine Device

Since the first description by Richter in 1909, the IUD has undergone many modifications (Hatcher et al. 1990). The types of IUDs currently available in Canada are the Gyne-T Cu 380® (Ortho Canada), the Nova-T® (Berlex Canada), and the Progestasert® (Alza Corporation). In 1984, the national survey on fertility for Canadian women (Balakrishnan et al. 1985) reported that the IUD was used as a contraceptive method by 8.3 percent of women. These women were primarily in the 25 to 44 age group; they were usually married and had a high level of education.





Cesarean section rates per 100 hospital deliveries in selected countries for 1985 or most recent year for which data were available (1981 through 1986 for Brazil, 1984 and 1985 for Puerto Rico and Canada, 1982 for Italy, 1987 for Portugal, 1983 for Greece, 1983 through 1986 for Switzerland and 1986 for Czechoslovakia). There was incomplete coverage of cesarean section rates for Australia, Bavaria, Portugal, Spain and Switzerland.

Cesarean rate for all births (including home births) was 6.0/100 births

Source: Ontario, Cesarean Birth Planning Committee, *Appropriate Use of Cesarean Section: Recommendations for a Quality Assurance Program* (Toronto: Ministry of Health, 1991), 5.

Table 17. International Cesarean Section Rates per 100 Deliveries

Country	1986	1987
Canada	18.9	18.7
Australia	16.6	16.6
Denmark	13.5	12.1
Hungary	10.1	10.2
Israel	10.1	10.2
Scotland	13.3	13.7
Yugoslavia	6.7	7.4
United States	n/a	24.4

Source: Ontario, Cesarean Birth Planning Committee, *Appropriate Use of Cesarean Section: Recommendations for a Quality Assurance Program* (Toronto: Ministry of Health, 1991), 5.

Table 18. Canadian Cesarean Section Rates

	Canada	Nfld.	P.E.I.	N.S.	N.B.	Que.	Ont.	Man.	Sask.	Alta.	B.C.
1969	5.2	4.3	5.4	5.1	5.0	4.6	5.9	4.0	4.4	4.4	6.1
1970	5.6	6.5	4.9	6.2	6.6	5.1	6.4	4.4	5.1	5.0	7.0
1971	6.4	7.5	4.0	6.7	6.6	6.1	6.8	5.1	5.5	5.3	7.8
1972	7.2	8.4	8.1	8.0	7.2	6.6	7.6	6.5	5.9	5.6	8.7
1973	8.8	10.0	8.2	9.0	7.2	7.6	8.4	6.9	6.6	6.7	9.4
1974	9.0	12.8	8.2	9.8	7.4	8.3	9.3	8.0	7.5	7.8	10.7
1975	9.6	12.8	9.5	10.8	9.0	9.0	9.7	8.3	7.8	8.4	11.6
1976	10.8	14.1	13.7	11.1	9.0	9.9	11.1	10.0	9.2	9.9	13.2
1977	12.1	14.8	13.7	11.9	11.6	11.5	12.3	10.4	11.1	11.0	14.2
1978	13.9	16.0	13.5	13.3	13.6	12.9	14.8	12.2	11.8	12.1	16.2
1979/80	14.7	18.3	15.5	15.5	14.6	12.9	15.9	14.4	11.8	13.3	16.6
1980/81	15.2	19.5	14.6	16.9	17.0	15.5	17.1	14.2	11.4	13.8	17.9
1981/82	16.6	18.9	17.0	16.9	17.0	16.4	17.4	14.8	12.6	14.1	18.8
1982/83	17.3	19.1	15.7	17.6	17.4	16.9	18.5	14.9	13.8	15.2	18.7
1983/84	18.1	20.2	14.5	18.2	19.1	18.2	19.0	14.9	14.3	15.6	20.0
1984/85	18.8	19.7	17.7	18.2	19.6	18.9	19.8	14.7	15.9	15.8	20.6
1985/86	18.9	21.4	17.4	18.0	19.0	19.3	20.2	14.7	15.9	16.5	19.9
1986/87	18.7	21.0	17.6	19.4	18.8	19.2	19.8	13.7	15.0	16.0	19.5

Rate per 100 deliveries
Source: Statistics Canada

Source: Ontario, Cesarean Birth Planning Committee, *Appropriate Use of Cesarean Section: Recommendations for a Quality Assurance Program* (Toronto: Ministry of Health, 1991), 6.

Table 19. Next Fertility-Related Event by Mode of Delivery in First Birth

Mode of delivery in first birth

	S	SVD		Inst.		CS		Total
Subsequent event	n	(%)	n	(%)	n	(%)	u	(%)
Pregnancy	8 888	(61.5)	3 706	(57.0)	940	(47.2)	13 534	(59.0)
Sterilization	241	(1.7)	124	(1.9)	54	(2.7)	419	(1.8)
None	5 319	(36.8)	2 677	(41.1)	666	(50.1)	8 995	(39.2)
Total	14 448	(100.0)	6 507	(100.0)	1 993	(100.0)	22 948	(100.0)

 $\chi^2 = 166.1$, d.f. = 4, P < 0.0001. SVD, Spontaneous vaginal

CS, caesarean section Inst., instrumental

Source: M.H. Hall et al., "Mode of Delivery and Future Fertility," British Journal of Obstetrics and Gynaecology 96 (1989), 1298.

First Birth
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Table 20.

•		2	Aode of deliv	Mode of delivery in first birth	irth			
Outcome	0,	SVD		Inst.		cs		Total
second pregnancy	п	(%)	п	(%)	и	(%)	и	(%)
Birth	7 745	(87.1)	3 197	(86.2)	793	(84.4)	11 735	(87.3)
Induced abortion	471	(5.3)	203	(5.5)	53	(5.6)	727	(5.4)
Miscarriage	672	(7.6)	306	(8.3)	94	(10.0) ^{a,b}	1 072	(7.9) ^b
Total	8 888	(100.0)	3 706	(100.0)	940	(100.0)	13 534	(100.0)
$^{a}Z = 2.61$, $P < 0.01$. $^{b}Z = 2.29$, $P < 0.05$. SVD, Spontaneous vaginal lnst., instrumental CS, caesarean section	aginal n							
Source: M.H. Hall et al., "Mode of Delivery and Future Fertility," British Journal of Obstetrics and Gynaecology 96 (1989), 1298.	t al., "Mode	of Delivery an	d Future Fert	illity," British Je	ournal of Obs	stetrics and Gyna	secology 96 (1989), 1298

Following the removal of the Dalkon Shield® (AH Robins Company) from the North American market, the IUD as a contraceptive device was frequently disparaged and difficult to obtain for most women (Tatum 1977; Hatcher et al. 1990). The IUD was also involved in the appearance of several pathologies that had an impact on fertility. We shall therefore review the role of the IUD in spontaneous abortion, ectopic pregnancy, PID, and infertility itself.

(a) IUD-Related Spontaneous Abortions

The risk of pregnancy for a woman in the first year of using the IUD is estimated at 0.5-2.0/100 woman-years (Hatcher et al. 1990). The universal recommendation when pregnancy occurs in a woman wearing an IUD is to remove it as soon as possible, preferably in the first trimester (Tatum 1977; Tatum and Connell 1986). If the woman wishes to proceed with the pregnancy and the IUD remains in place, the risk of miscarriage is approximately 50 percent, whereas it declines to 25 percent if the IUD is removed (ibid.). Close clinical follow-up is recommended for women who wish to proceed with pregnancy but for whom it was impossible to remove the IUD; these women may in fact develop chorioamnionitis, which may affect the child's health as well as the health and subsequent fertility of the mother; the incidence of this phenomenon is very low and has not been measured (Tatum and Connell 1986).

(b) IUD-Related Ectopic Pregnancies

In the United States, the incidence of ectopic pregnancy has increased steadily from the 1960s to the present (Table 21). The same phenomenon has been observed in Quebec, with a 39 percent increase in hospitalizations due to ectopic pregnancies from 1984 to 1988 (Rochette 1991b). While one ectopic pregnancy was reported in the United States for every 253 pregnancies in 1965, the ratio in 1982 was 1/91 (Sivin 1985). In industrialized countries, the highest rates of ectopic pregnancy are found in women aged 25 to 34 years (ibid.), and this is also the case in Quebec (Rochette 1991b).

As shown in Tables 22, 23, and 24, the rate of ectopic pregnancy per 1 000 woman-years varies from 0.0 to 1.4 for women who use plastic or copper IUDs, and from 0.0 to 11.3 for women who use progesterone IUDs (Sivin 1985). According to the theoretical model put forward by Franks et al. (1990), a comparison of ectopic pregnancy risk for women who do not use any contraception with those who do leads to the following conclusions (Table 25): the incidence of ectopic pregnancy in women using the IUD is 2.5 times lower than for sexually active women who use no contraception. The incidence of ectopic pregnancy in women using the IUD is approximately 102/1 000 woman-years, which is 10 times higher than for women whose partners use condoms and 200 times higher than for women who use oral contraceptives. The results of a multicentre case-control study carried out by the World Health Organization confirm the protective effect of the IUD when compared to the absence of any form of contraception (Gray 1985). This study also highlights the fact that the IUD provides less

protection from ectopic pregnancy than any other method of contraception. The study shows as well that a history of PID and of ectopic pregnancy are important risk factors in ectopic pregnancy (ibid.). There is, however, no evidence that the use of an IUD increases the subsequent risk of ectopic pregnancy in a woman who has already experienced one (Sivin 1985). Likewise, no link was found between the risk of ectopic pregnancy and the length of time an IUD is used, but the scientific literature on this particular subject is limited (ibid.; Tatum and Connell 1986). The use of an IUD does not result in ectopic pregnancy.

(c) IUD-Related Pelvic Inflammatory Disease

Pelvic inflammatory disease, which is defined as a supracervical infection of the uterus, the fallopian tubes, and the ovaries, is a serious health problem in many countries. The incidence of PID increased between 1960 and 1980 in the United States, the United Kingdom, and Sweden (Weström 1980; Gray and Campbell 1985). The incidence of PID in the United States in the early 1980s was estimated at 2/100 woman-years (Struthers 1987; Mumford and Kessel 1989b). In Quebec, the prevalence of PID calculated on the basis of diagnoses calling for hospitalization was 0.151/100 woman-years for the period from 1984 to 1988 (Rochette 1991a). The decrease observed in Quebec statistics from 1984 to 1988 has not yet been explained: we do not know whether there was a genuine decrease in the prevalence of PID or whether doctors did not require women to be hospitalized for the condition with the same frequency (ibid.). Pelvic inflammatory disease affects primarily women 15 to 25 years of age (Weström 1980; Gray and Campbell 1985; Rochette 1991a). It is in women under 20 years of age that the incidence of PID has increased most over the past 20 years (ibid.).

Pelvic inflammatory disease is known to be a significant infertility risk factor: the risk increases with the number and severity of occurrences (Weström 1975, 1980). The risk of infertility is estimated at 11 percent after a single PID occurrence, at 23 percent after two occurrences, and at 54 percent after three occurrences (Weström 1975).

Of the many reasons given to explain the increase in the incidence of PID, the increased use of the IUD was put forward by several researchers. This association is the main reason for the decline in the popularity of IUDs in North America (Tatum 1977; Weström 1980; Gray and Campbell 1985; Tatum and Connell 1986). A review of the literature (Mumford and Kessel 1989b) on studies concerning the risk of PID in IUD users made it possible to identify:

- 71 clinical trials, of which 25 were non-randomized follow-up comparative studies and 7 experimental studies (comparing several different types of IUDs);
- 16 case-control studies; and
- 2 cohort studies.

Table 21. Annual Incidence of Ectopic Pregnancy per 1 000 Women Aged 15 to 44 Years

			Sweden	
Years	England and Wales	United States	Lund*	Uppsala
1960-1964			0.57	0.27
1965-1969	0.29	0.39	0.76	0.39
1970-1974	0.35	0.51	0.09	0.72
1975-1979	0.33	0.78	1.17	1.06
1980		0.90		
1981		1.13		
1982		1.09		

^{*} Lund data on women aged 15 to 39 years.

Source: I. Sivin, "IUD-Associated Ectopic Pregnancies, 1974 to 1984," in *Intrauterine Conception: Advances and Future Prospects*, ed. G.I. Zatuchni, A. Goldsmith, and J.J. Sciarra (New York: Harper and Row, 1985), 341.

Table 22. IUD Ectopic Pregnancy Rates per 1 000 Years of Use

Randomized international studies 1974-1983							
Sponsor	Drug	Number of ectopics	Woman-years (in hundreds)	Rate per 1 000 woman-years			
WHO	Copper	5	123	0.4			
	Plastic	2	28	0.7			
	Progest 25	4	18	5.2*			
FHI	Copper	0	13	0			
PC	Copper	0	6	0			
	LNG 20	0	6	0			
		Straight Interna	tional Study				
Alza	Progest 65	53	101	5.2			

^{* 5.2} is 2-year gross rate; Pearl index is 2.2 per 1 000.

Source: I. Sivin, "IUD-Associated Ectopic Pregnancies, 1974 to 1984," in *Intrauterine Conception: Advances and Future Prospects*, ed. G.I. Zatuchni, A. Goldsmith, and J.J. Sciarra (New York: Harper and Row, 1985), 345.

Location	Drug	Number of ectopics	Woman- years (in hundreds)	Rate per 1 000 woman- years
Scandinavia	Progesterone*	5	4	11.3
	Copper	10	74	1.4
Belgium/Netherlands	Copper	7	100	0.7
United Kingdom	Copper	1	7	1.4
	Plastic	16	145	1.1
United States/Canada	Progesterone*	26	46	5.6
	Copper	5	61	0.8

^{* 65} μg/day.

Source: I. Sivin, "IUD-Associated Ectopic Pregnancies, 1974 to 1984," in *Intrauterine Conception: Advances and Future Prospects*, ed. G.I. Zatuchni, A. Goldsmith, and J.J. Sciarra (New York: Harper and Row, 1985), 345.

Table 24. IUD Ectopic Pregnancy Rates 1974-1983. Device-Specific Summary

Drug and	d device	Number of studies	Woman- years	Rate per 1 000 woman-years
Copper	TCu 200	5	4 836	1.4
	Cu7	6	5 490	0.9
	Nova T	3	2 668	0.7
	TCu 220	7	11 931	0.8
	MLCu 250	4	8 207	0.2
	Fincoid	1	835	1.2
	MLCu 375	1	637	0.0
	TCu 380	3	1 929	0.0
Plastic	Lippes Loop C & D	4	12 621	1.1
	Saf-T-Coil	1	4 712	0.8
Steroids	Progestasert	1	10 128	5.2
	LNG 20 μg	2	893	1.1

Source: I. Sivin, "IUD-Associated Ectopic Pregnancies, 1974 to 1984," in *Intrauterine Conception: Advances and Future Prospects*, ed. G.I. Zatuchni, A. Goldsmith, and J.J. Sciarra (New York: Harper and Row, 1985), 346.

Table 25. Estimated Incidence Rates of Ectopic Pregnancy by Contraceptive Method

Contraceptive method	Lowest expected pregnancy rate per 1 000 woman-years* (A)	Proportion ectopic implantation* (B)	Estimated ectopic pregnancy incidence rate per 1 000 woman-years (A × B)
Oral contraceptive [†]	1	0.005	0.005
Vasectomy	1	0.005	0.005
Condom	20	0.005	0.100
Diaphragm	30	0.005	0.150
Tubal sterilization	2	0.159	0.318
IUD [‡]	20	0.051	1.020
None	520	0.005	2.600

^{*} See material and methods section [in text of original article] for origin of these numbers

Source: A.L. Franks et al., "Contraception and Ectopic Pregnancy Risk," *American Journal of Obstetrics and Gynecology* 163 (1990), 1121.

It is important to mention the scientific superiority of the experimental studies compared to any other research procedures. They are not subject to important methodological biases that plague case-control studies (Edelman 1985; Mayes et al. 1988; Mumford and Kessel 1989a, 1989b; Kronmal et al. 1991), such as the following:

- detection bias, which leads to a higher probability of PID diagnosis in IUD wearers;
- control groups including women who use oral contraceptives or barrier methods, which protect against the movement of STDs toward the upper genital tract;
- confounding bias related to the sexual activity of the women involved; and
- reference bias leading to a higher probability of referring women who wear IUDs to a hospital for PID.

Certain biases also affect cohort studies (detection bias, reference bias, diagnostic bias, and information bias) (Mumford and Kessel 1989a).

As Table 26 shows, the relative risks of PID associated with the use of IUDs in 16 case-control studies and 2 cohort studies varied from 8.3 to 78.7 in users of the Dalkon Shield $^{\otimes}$ and from 1.5 to 10.8 in users of other types of IUDs (Mumford and Kessel 1989b). The results show that studies

[†] Combination estrogen-progestin only.

[‡] Unmedicated only.

carried out on a higher number of cases report relatively lower risks. Among the clinical trials surveyed, two simple trials reported the occurrence of PID: the incidence of PID was 4.8 percent in one (the clinic also reported a 5 percent prevalence of gonorrhoea) and it was not significant in the other. Eleven non-randomized comparative clinical trials also reported PID: four studies reported only one case or no significant inflammation. The PID rate in the year following insertion of the IUD was 1 to 3 percent in six studies; only one study reported a rate varying from 0.6 to 13.2, with the increase coming when the Dalkon Shield® case hit the media (ibid.). Three of the seven randomized comparative studies reported their PID rates in the year following the insertion of the IUD, which varied from less than 1 percent to 3 percent (Gray and Campbell 1985).

In a recent study undertaken by the World Health Organization, Farley et al. (1992) demonstrated that the risk of pelvic infection following IUD insertion represented 1.6 cases per 1 000 woman-years of use. After adjusting for confounding factors, this risk was six times higher than that in the first 20 days following insertion. Beyond that period, the risk was low and remained constant in the following eight years. This international study, covering 22 968 IUD insertions and over half a million cycles of use, enabled the identification of certain PID risk factors: beyond geographical variations, risk increased inversely to age and parity. Women whose IUD had been inserted after 1980 showed less pelvic infection than those whose IUD had been inserted prior to that date (improved aseptic techniques and user selection over the years). The authors conclude that exposure to STDs, often encountered in young women who have never given birth before, is the main factor causing pelvic infection following IUD insertion. They recommend carefully monitoring women in the first 20 days following IUD insertion and not replacing IUDs needlessly. It would therefore appear that, in general, the most valid studies reported a PID rate for women using IUDs that was close to that for women in general.

Nevertheless, experts agree that there is an increased risk of PID in the one to three months following IUD insertion (Defoort 1985; Keith and Berger 1985; Farley et al. 1992). The risk depends on several factors, such as the aseptic technique used in inserting the IUD, the doctor's experience, the bacteria present in the woman's vagina during insertion, and the woman's immunological defences. We have not found any studies that evaluated the importance of these factors in connection with the risk of PID related to IUD insertion.

To summarize, the majority of researchers now agree that the use of the IUD itself is responsible for only a very low percentage of PID occurrences, and that these are primarily linked to insertion procedures (Defoort 1985; Edelman 1985; Gray and Campbell 1985; Keith and Berger 1985; Tatum and Connell 1986; Mumford and Kessel 1989a, 1989b; Kronmal et al. 1991; Farley et al. 1992). On the other hand, all researchers recognize that the IUD does not play a role in protecting against PID, as do other contraceptive methods. As a result, the use of the IUD should be

Table 26. Case-Control and Cohort Studies of IUDs: Estimated Relative Risks (RR) of Pelvic Inflammatory Disease (PID) for Current IUD Use

						Estimated RR (unadiusted)
Reference/dates of study	Study location	Number of non-IUD controls	Number of IUD controls	Number of non-IUD cases	Number of IUD cases	and 95% confidence interval
Case control studies						
Thaler et al. (74) 1969-70	Haifa, Israel	94	7	98	15	2.3 (0.9-6.0)
Lippes (75) 1972-73	Buffalo, USA	35	ෆ	78	13	1.9 (0.5-7.3)
Targum and Wright (76) 1973	New York, USA	91	26	6	24	9.3 (3.9-22.5)
Faulkner and Ory (77) not stated	Atlanta, USA	178	22	31	19	5.0 (2.4-10.2)
Weström et al. (78) 1971-75	Lund, Sweden	099	72	390	125	2.9 (2.1-4.0)
Eschenbach et al. (79) 1972-74	Seattle, USA	273	31	143	61	3.8 (2.3-6.1)
		(Using VD c	(Using VD clinic patients for controls)	or controls)		
		329	9/	143	61	1.8 (1.3-2.7)
		(Using OB c	(Using OB clinic patients for controls)	or controls)		
Flesh et al. (80) 1976	Los Angeles, USA	192	30	122	41	2.2 (1.3-3.6)
Osser et al. (81) 1973-75	Malmö, Sweden	929	114	470	220	2.4 (1.8-3.1)
Ryden et al. (82) 1973-77	Linkoping, Sweden	154	20	29	20	2.3 (1.2-4.6)
Kaufman et al. (83) 1976-78	Urban Hospitals,	172	87	14	30	4.2 (2.1-8.4)
	and Israel	172	5	14	5	12.3 (3.2-47.6)
					(Dalkon	

	7.4 (3.9-14.1)	34 (Dalkon Shield)	245	41	750		
	1.4 (1.1-1.8)	147 (other IUDs)	245	317	750	Urban Hospitals, USA	Lee et al. (14) 1976-78
	24.0 (5.1-112.2)	11 (Dalkon Shield)	44	0	192		
	4.9 (3.2-7.6)	104 (all IUDs)	44	95	192	Urban Hospitals, USA, Canada	Kaufman et al. (87) 1976-81
	4.0 (2.4-6.5)	49 (developed countries)	104	33	277		
	2.0 (1.4-2.7)	80 (developing countries)	327	92	735	4 developed and 8 developing country centers	WHO (86) 1978-79
	7.1 (3.8-13.3)	35 (Dalkon Shield)	250	15	763		
	1.7 (1.3-2.1)	185 (all IUDs)	250	337	763	Urban Hospitals, USA	Lee et al. (13) 1976-78
	3.0 (1.9-4.6)	83	61	72	157	Helsinki, Vesterinen	Paavonen and Finland (85) 1977-78
<i>-</i>	1.6 (1.4-1.9)	318	621 1	218	2 935	USA USA	

Estimated RR (unadjusted)

and 95% confidence

interval

57.8³

10.82

1.54

Reference/dates of study	Study location	Number of non-IUD controls	Number of IUD controls	Number of non-IUD cases	Number of IUD cases
Cohort studies					
Vessey et al. (88) 1968-79	Oxford, England	65 2591	20 4821	6	31 (all IUDs)
					3 (Dalkon Shield)
Weström et al. (7) 1970-74	Lund, Sweden	5 0321	2 9351	172	153

Woman-years of observation.

² Incidence of PID for IUD-users = 0.151 and for non-users = 0.014. Therefore RR = 0.151/0.014 = 10.8.

³ RR for Dalkon Shield = 0.809/0.014 = 57.8.

4 Incidence of PID for IUD-users = 0.0521 and for non-users = 0.0342. Therefore RR = 0.0521/0.0342 = 1.5.

Note: Please consult table source for complete bibliographic details.

Source: S.D. Mumford and E. Kessel, "Dalkon Shield: The Perfect Conflict Between Case-Control and Clinical Trial Study Findings" (Research Triangle Park: Center for Research on Population and Security, 1989), Table 1.

Table 27. Possible Contraindications to Use of Intrauterine Devices

Absolute contraindications:

- Active, recent or recurrent pelvic infection (acute or subacute), including known or suspected gonorrhea or chlamydia
- 2. Pregnancy (known or suspected)

Strong relative contraindications:

- 3. Risk factors for PID:
 - postpartum endometritis
 - · infection following an abortion that occurred in the past 3 months
 - purulent cervicitis, until controlled
 - impaired response to infection (diabetes, steroid treatment)
 - · recurrent history of gonorrhea
 - high risk for a sexually transmitted disease, including multiple sexual partners or a partner who has multiple sexual partners
- 4. Undiagnosed, irregular, or abnormal uterine bleeding
- 5. Risk factors for exposure to the human immunodeficiency virus (HIV)
- Cervical or uterine malignancy (known or suspected), including unresolved Pap smear
- 7. History of ectopic pregnancy
- 8. Impaired coagulation response (idiopathic thrombocytopenic purpura, anticoagulant therapy, etc.)
- 9. Previous problems with IUD pregnancies or expulsion
- Impaired ability to check for danger signals (i.e., unable to check for IUD string)
- 11. Past history of severe vasovagal reactivity or fainting
- 12. Emergency treatment difficult to obtain

Other possible relative contraindications include:

- valvular heart disease, which may make the patient susceptible to subacute bacterial endocarditis (some clinicians recommend prophylactic antibiotics);
- anatomical difficulties such as an abnormal shape (leiomyomata, endometrial polyps, bicornuate uterus), cervical stenosis, or a small uterus;
- menstrual disorders such as severe dysmenorrhea, severe menorrhagia, or endometriosis:
- anemia, history of impaired fertility in a woman who desires a future pregnancy;
- history of fainting;
- an allergy to copper or diagnosed Wilson's disease

Source: R.A. Hatcher et al., *Contraceptive Technology, 1990-1992*, 15th rev. ed. (New York: Irvington, 1990), 361.

reserved for women for whom the PID risk is very low. A list of contraindications to the use of the IUD is given in Table 27. As well, IUDs should be left in place for the maximum length of their efficiency (at least eight years for those containing 380 mm² of copper) for as long as women require them and insofar as the women are not at risk of being exposed to STDs. Finally, women should be carefully monitored during the first 20 days following insertion.

(d) IUD-Related Infertility

The association of the IUD with infertility is one of the factors that led to its low popularity. As Struthers mentioned, it is striking to note that, in the United States in 1982, Hispanic women, who, when compared to Black or Caucasian women, are the greatest users of the IUD, are also those who consult infertility clinics the least (Struthers 1987).

The earliest studies on return of fertility following the use of the IUD are mentioned by Tatum and Connell (1986). They indicate that there is no reduction in fertility in women who have the IUD removed in order to conceive. This finding was confirmed by follow-up studies (Rioux et al. 1986; Struthers 1987; Gupta et al. 1989; Huggins and Cullins 1990), such as the ones comparing the return of fertility after the use of various contraceptive methods (Table 28).

On the other hand, two case-control studies contradict these results. Daling et al. (1985) compared 159 women whose infertility was primarily due to fallopian tube problems to 159 women, comparable in terms of age and race, who had conceived their first child at a time when the other women were being treated for infertility. Tobacco smoking, the number of sexual partners, and income were controlled. The researchers reported a primary infertility risk 2.6 times higher in users of the IUD compared to non-users. The risk varied from 6.8 to 11.3 (significant) in users of the Dalkon Shield®, whereas it was 1.3 to 1.9 (not significant) in users of copper IUDs. Cramer et al. (1985) compared 283 women with fallopian tube primary infertility and 69 women experiencing secondary infertility to 3 833 women admitted for delivery in seven hospitals. Region of origin, date of first menstruation, religion, education, and number of sexual partners were controlled in the study. The authors found a risk of primary infertility 2.0 times higher in users of the IUD compared to non-users. The risk was 3.3 times higher for users of the Dalkon Shield® and only 1.6 times higher for users of copper IUDs. Cramer et al. (1985) nevertheless reported that the risk of primary infertility did not increase in women who had only one sexual partner and who used a copper IUD. Likewise, the risk of secondary infertility in copper IUD users was 1.5, which is not significant, while it was 2.8 in plastic IUD users. In view of the results of these two studies (ibid.; Daling et al. 1985), it is important to underline the potential biases:

• recall bias, with the women being studied remembering more than others as to whether they had used an IUD;

Table 28. Return to Fertility

	Tin		stopping onths)	use	
o	12	24	36	48	Reference
IUD, age <30	88.6	93.6		96.6	Randic et al.
age ≥30	78.4	86.0	_	88.0	[10]
IUD, used <24mo	80.7	91.6	94.4		Pyörälä <i>et al.</i>
used ≥24mo	73.1	85.7	85.7		[11]
Nova T	72.0	85.5	91.5		
Cu T	83.8	96.8			
IUD	51.2	89.4	93.3		Vessey et al.
OC	39.3	89.2	95.4		[12]
diaphragm	86.2	91.8	93.8		

Note: Please consult table source for complete bibliographic material.

Source: B.J. Struthers, "Sexually Transmitted Disease, Infertility, IUDs and Epidemiology," *Advances in Contraception* 3 (1987), 85.

 confounding bias, related to the previous use of contraceptive methods that protect against PID, or to the earlier acquisition of STDs or PID.

Rioux et al. (1986) disagree with the above authors: they found the return of fertility identical in women who used a copper IUD and women who used the Dalkon Shield[®].

To summarize, in light of these studies, no causal link can be established between the use of the IUD and infertility. On the other hand, there appears to be no doubt that infertility is related to the number of sexual partners and to exposure to STDs and to PID. The same recommendations that were made concerning the selection of low PID risk women as candidates for the IUD therefore also hold with respect to preventing infertility.

Cervical Procedures

Cervical Surgery

Cervical surgery has an impact on female fertility — defined as the capacity to maintain pregnancy to term — insofar as it may lead to, among other conditions, an incompetent cervix during pregnancy.

An incompetent cervix, which was recognized in the early twentieth century, is defined as the inability to maintain intrauterine pregnancy to term, either because the cervical structure is inadequate or because it does not function properly (Thomason et al. 1982). Cervical traumas are considered responsible for 30 to 50 percent of cases of incompetent cervix.

These traumas can occur when surgery is performed (D&C, dilatation-evacuation, medically induced abortion, conization of the cervix, cervical amputation), in natural delivery, or when certain implements or procedures are used during delivery (forceps, Durhssen incision). The second cause of an incompetent cervix is congenital anatomic abnormalities of the woman's genital tract. Lastly, diethylstilbestrol has also been associated with this condition. For information purposes, we note that surgery is required to treat an incompetent cervix, and it consists of cerclage of the cervix (through suture); without this treatment, the fetal survival rate is approximately 20 to 50 percent, whereas it is 70 to 90 percent when cerclage is performed (ibid.).

Because the data concerning abortion techniques and infertility as a result of medical procedures are given in the subsection on induced abortion, we shall discuss only cervical dilatation here. To decrease abortion morbidity, the method of cervical dilatation is perhaps more important than the evacuation method (Ott 1977). The supravaginal part of the cervix is especially vulnerable, because it generates the greatest resistance during dilatation. Many lesions would seem to result from excessive force used with dilatation instruments. The cervix is easier to dilate as the pregnancy advances, because it becomes progressively softer; on the other hand, a soft cervix can more easily be lacerated by cervical forceps; also, the further advanced the pregnancy, the greater the required dilatation. The incidence of cervical trauma following induced abortion is estimated at 0.0 to 5.0 percent; the various definitions of these trauma and their seriousness make it impossible to assess satisfactorily the extent of the problem. Papers discussing connections between forced cervical dilatation and an incompetent cervix are not conclusive either: they report contradictory facts and suffer from methodological shortcomings. In any case, researchers agree that more suitable instruments (Pratt rather than Hegar dilator) or alternative techniques (laminaria, prostaglandins, antiprogesterone) should be used to dilate the cervix (ibid.).

There are very few papers on cervical conization and infertility. It is reported that women who undergo a cervical conization may experience stenosis of the external cervical opening, an absence of cervical mucus in mid-cycle, and the failure of the cervix to open during ovulation (March 1985). It is also reported that cervical conization may reduce fertility and increase the risk of incompetent cervix and premature delivery (Jones et al. 1979; Buller and Jones 1982; March 1985). Authors agree, however, that colposcopy and the use of less radical conizations offer a solution to the potential problems caused by traditional conization.

Use of Laminaria

Laminaria (which absorb water and swell) were used traditionally to dilate the cervix in cases of primary infertility and dysmenorrhoea (Ott 1977; Darney 1986; Johnson 1989). They virtually disappeared from medical practice in the early twentieth century in North America because of associated infection problems (Ott 1977; Stubblefield 1988). Modern

aseptic techniques made it possible to reintroduce them. Laminaria are now regularly used to dilate the cervix prior to induced abortion, to induce delivery in the second and third trimester, and for any other procedures requiring cervical dilatation or even urethral dilatation (ibid.).

There are three types of laminaria: natural (stipes of *Laminaria digitata* and *Laminaria japonica*), the Lamicel (polyvinyl alcohol sponge impregnated with 450 mg of magnesium sulfate), and the Dilapan (derived from hypan, a hydrophilic compound, an acrylonitrile polymer). These are inserted in the cervix and dilate it by absorbing water from the cervical stroma; they swell and apply moderate radial force to the walls of the cervical canal. Maximum dilatation is obtained in 3 to 18 hours, depending on the type of laminaria used and the degree of dilatation required.

The short-term benefits of using laminaria are known: decreased risk of uterine perforation and cervical trauma during induced abortion in the first or second trimester (Ott 1977; Cates et al. 1983; Darney 1986; Johnson 1989), decreased bleeding and operating time, and a lower risk of major post-abortion surgery (Gold et al. 1980; Johnson 1989). The Joint Program for the Study of Abortion/Centers for Disease Control, in a multicentre study on induced abortion in the first trimester in a hospital, found that infectious morbidity was lower in 3 260 women on whom dilatation had been performed with laminaria, compared to 26 500 women on whom dilatation had been performed using rigid dilators (Gold et al. 1980). It is thought that the use of laminaria during induced abortion or other procedures may reduce the risk of cervical incompetence and hence second-trimester abortion in a subsequent pregnancy; however, no longterm experimental studies document this claim (Johnson 1989). Nor is it known if the use of Dilapan, which produces cervical dilatation very quickly, causes cervical damage (Darney 1986).

The complications reported in the use of laminaria (Darney 1986; Johnson 1989) include cervical tears, uterine perforations, entrapment (Johnson 1988), migration, fragmentation (Gusdon and May 1975), expulsion, false labour, rupture of the amniotic sac, and one fetal death (Agress and Benedetti 1981). The incidence of these complications is extremely low, and they are all isolated cases. None of the studies we reviewed indicated any link between the use of laminaria and infertility, defined as the incapacity to conceive.

Induced Abortion

In Canada in 1988, there were 66 251 reported induced abortions, which corresponds to a rate of 10.6 abortions per 1 000 women in the 15 to 44 age group, and a ratio of 176 abortions per 1 000 live births. The number of abortions in Canada increased from 1970 to 1978 and then stabilized (Canada, Statistics Canada 1990b). This was not the case in all provinces, however, as shown by the data reported for Quebec and Manitoba, where the number of abortions and the abortion rates have increased steadily since 1970, particularly for women under 25 years of age (Rochon 1989a; Canada, Statistics Canada 1990b).

Young women represent the sector of the population most likely to have an abortion, and the highest rates were found in the 18 to 19 and 20 to 24 age groups. In 1988, 76.3 percent of Canadian women who obtained an abortion were under 30 years of age (Canada, Statistics Canada 1990b).

Abortion is one of the most frequently performed surgical procedures (Quebec, Régie de l'assurance-maladie du Québec 1989). Given that it primarily affects the younger members of the population, it is of interest to measure its impact on the fertility of the women who have abortions performed.

Reports and studies on abortion methods and on mortality and morbidity associated with them will therefore be discussed. Studies specifically concerning the relationship between abortion and various aspects of infertility will also be examined. The impact of repeated abortions will be analyzed in a special section.

In this subsection, the term "abortion" will essentially refer to abortions that are induced, for whatever reason. It is worth noting that most abortions these days are obtained for psychosocial reasons (Guilbert 1991).

(a) Abortion Techniques

There are several different abortion techniques. Suction curettage was by far the most widely used method for first-trimester abortions in Canada and throughout the world in the 1980s (Tietze and Henshaw 1986; Canada, Statistics Canada 1990b). Suction-evacuation-curettage, a variant of the above method, may be used up to the twenty-sixth week of gestation. The two methods are now preferred to the classic D&C procedure, which can be practised up to the sixteenth week of gestation (Stubblefield 1986; Tietze and Henshaw 1986).

Medical induction techniques are also used, specifically in second-trimester abortions. The main substances used to trigger this type of abortion are saline solution, urea, and prostaglandins.

Lastly, a very small number of abortions are performed by means of hysterotomy and hysterectomy. The number of such abortions dropped significantly from 1975 to 1988 in Canada and elsewhere in the world. In industrialized countries, hysterectomy abortions in the 1980s accounted for 0.1 to 1.0 percent of procedures (Tietze and Henshaw 1986; Canada, Statistics Canada 1990b). Of the 66 137 abortions in Canada in 1988, 17 used these procedures (Canada, Statistics Canada 1990b).

(b) Abortion-Related Mortality

As the American College of Obstetricians and Gynecologists reported in January 1990, "Today, abortion is one of the safest surgical procedures in the United States" (Moore 1990). The mortality risk from a tonsillectomy is twice as high, and from an appendectomy one hundred times as high, as the mortality risk from abortion.

From 1975 to 1980, only one abortion-related death was reported by Statistics Canada (Wadhera 1982). None has been recorded since 1980 (Canada, Statistics Canada 1990b). According to American statistics, the

mortality rate went from 2.3/100 000 in the 1972-1978 period to 0.8/100 000 in the 1979-1985 period (Atrash et al. 1990). The mortality rate is higher in countries where abortion is illegal or difficult to obtain (Henshaw 1990).

Since 1979, any deaths following abortions have been primarily related to anaesthesia (Atrash et al. 1990). The other causes of death vary with age, with younger women showing a higher incidence of death from infection (Cates 1980).

Abortion-related mortality risk factors include age of the patient (older women), race (Blacks), ethnicity (ethnic minorities), length of gestation (advanced), and the abortion method used (medical induction, hysterectomy, hysterotomy) (Cates 1980; Atrash et al. 1990). The same risk factors are found for post-abortion death from pulmonary embolism (Lawson et al. 1990) and for most abortion complications.

Two main factors have contributed to the decreased abortion mortality

rate:

 the shorter gestation period at the time of abortion, owing to improved access to services;

• the use by doctors of the suction curettage technique, with or without evacuation, up to the sixteenth week of gestation (Binkin 1986; Atrash et al. 1990).

(c) Abortion-Related Morbidity

The rate of complications resulting from abortion depends a great deal on the definition of the pathologies considered. Although incomplete, Statistics Canada data show that the rate of major complications (haemorrhaging requiring at least one transfusion, infection including at least two days of fever (40°C peak) or hospitalization of 11 days or more, major unexpected surgery) dropped from 3.2 percent in 1975 to 1.6 percent in 1988 (Wadhera 1982; Canada, Statistics Canada 1990b). In England, among the 6 105 women who had an abortion between 1976 and 1979, 2.1 percent suffered major complications (Royal College of General Practitioners and Royal College of Obstetricians and Gynaecologists 1985). investigations concerning the incidence of serious post-abortion complications reported rates of 1/200 in 1970-1971 (Tietze and Lewit 1972), 1-2/1 000 abortions in 1975-1978 (Cates 1980), and 0.71/1 000 in the 1971-1987 period (Hakim-Elahi et al. 1990). In spite of methodological biases, particularly in connection with patient follow-up, it may be stated that major complications following abortion are rare.

(d) Abortion-Related Secondary Hysterectomies

Of these major complications, the one that is most significant in connection with the risk of infertility is secondary hysterectomy. Secondary hysterectomies, which generally follow a massive haemorrhage or a major uterine perforation, are rare following abortion. In the study carried out by the Joint Program for the Study of Abortion (Tietze and Lewit 1972), 57 hysterectomies were reported, a rate of 3.5 per 10 000 procedures; the

number increases with the age of the woman and the number of children borne previously. In the British study mentioned in the previous section (Royal College of General Practitioners et al. 1985), out of 6 105 procedures only one hysterectomy was reported. Lastly, in Canada, 28 secondary hysterectomies were performed from 1976 to 1980, a rate of 0.9/10 000 abortions (Tietze and Henshaw 1986).

(e) Abortion-Related Endometrial Synechias

Not much is known about the incidence of these lesions. Endometrial synechias, better known as Asherman's syndrome, may occur in the endocervix or in the uterine cavity. They are a cause of infertility and essentially result from trauma. Two-thirds of all cases of Asherman's syndrome follow a curettage during an abortion, a spontaneous abortion, or a pregnancy carried to term (March 1985). Synechias appear more often when the curettage is performed two to four weeks following delivery. It would appear that the suction curettage technique is less traumatic than simple curettage (ibid.).

Two studies on the same population report Asherman's syndrome in 28 cases out of 170 000 abortions (Hakim-Elahi et al. 1990) and in 12 cases out of 25 000 (Hakim-Elahi 1976). In another study reported by March (1985), endometrial synechias appeared in 27/275 women who had had an abortion, uterine synechias appeared in 20/275, and synechias in both locations in 16/275. Lastly, in a population of 118 women who had undergone an abortion, French researchers found synechias in 25 women two weeks after the abortion and in none two weeks later (Salat-Baroux et al. 1984).

Before the advent of the hysteroscopy, treatment of Asherman's syndrome resulted in a subsequent pregnancy rate of 30 to 60 percent (March 1985). The hysteroscopy has made it possible to increase the post-treatment pregnancy rate to 87 percent (ibid.; Huggins and Cullins 1990) (Table 29).

(f) Abortion-Related Pelvic Inflammatory Disease

There is a known relationship between PID and infertility. The risk of infertility increases with the number of occurrences of PID and their severity (Table 30). Infection is the second most frequent delayed complication following an abortion (Grimes and Cates 1979). Lack of consistency in defining and providing diagnostic criteria for PID makes it difficult to interpret data concerning its incidence. An incidence of 38°C fever for a day or more following abortion occurs in 0.75 percent of women who undergo an abortion. For abortions in the thirteenth to twentieth weeks, whether by vacuum-evacuation-curettage, saline solution, or prostaglandins $F2\alpha$, the risk of PID is, respectively, 1.34 percent, 4.99 percent, and 10.8 percent (ibid.). The incidence of post-abortion PID varies from 0.18 to 5.0 percent, depending on the study (Burnhill et al. 1977; Cates 1980; Wadhera 1982; Royal College of General Practitioners et al.

Table 29. Gestational Outcome After Treatment for Intrauterine Adhesions^a

Method	Pregnancies (n)	1-2 trimester losses	Term %
Traditional	369	104 (28)	147 (40)
Sugimoto (85)*	79	29 (37)	45 (57)
USC (50)*	62	8 (13)	54 (87)

- Traditional includes blind disruption of adhesions and is gathered from the literature. USC, University of Southern California data, corrected to eliminate losses secondary to known causes (e.g. elective abortion, cervical incompetence).
- Please consult original source for complete bibliographic details.

Source: C.M. March, "Intrauterine and Cervical Pathology," in *Surgical Treatment of the Infertile Female*, ed. V.C. Buttram, Jr. and R.C. Reiter (Baltimore: Williams and Wilkins, 1985), 268.

Table 30. Percent of Infertility Because of Tubal Occlusion After One, Two, and Three or More Episodes of Salpingitis in Women Exposed to a Chance of Pregnancy

	% infertility	postsalpingitis in	age group
No. of infections	15 to 24 yr	25 to 34 yr	Total
1	9.4	19.2	11.4
2	20.9	31.0	23.1
3+	51.6	60.0	54.3

Source: L. Weström, "Incidence, Prevalence and Trends of Acute Pelvic Inflammatory Disease and Its Consequences in Industrialized Countries," *American Journal of Obstetrics and Gynecology* 138 (1980), 888.

1985; Binkin 1986; Freedman et al. 1986; Heisterberg 1988; Levallois and Rioux 1988; Hakim-Elahi et al. 1990). These figures are strongly influenced by the personal history of the women concerned in terms of STD and PID, as well as by whether or not they were infected by a STD at the time of abortion.

Pre-abortion diagnosis of STDs and a prophylactic antibiotic therapy for PID can diminish the risk of infection by up to 87 percent (Darj et al. 1987; Heisterberg 1988; Levallois and Rioux 1988).

In conclusion, abortion-related infection is a risk and has been known to lead to infertility in certain cases. However, the risk can be minimized by using appropriate preventive measures (diagnosis, prophylaxy).

(g) Abortion-Related Rh Iso-Immunization

Abortion is the second most frequent cause of Rh iso-immunization. In some studies, it was found that the percentage of women sensitive to the Rh factor during abortion could be as high as 5 to 10 percent (Grimes and Cates 1979). Grimes and Cates reported a study in which the risk of sensitivity to the Rh factor was assessed at 0 percent for abortions occurring in the first month of gestation, 2 percent for those occurring in the second, and ±9 percent for those occurring after three months.

As noted by Cates (1980) and Tietze and Henshaw (1986), all Rhnegative women who are not sensitive should receive Rh immunoglobulins. In spite of this recommendation, made by many agencies, the practice is reported in 42 to 99 percent of women who need it (Grimes and Cates 1979).

(h) Impact of Abortion on Fertility

There are many studies and literature reviews on this subject. The review by Hogue and colleagues, carried out in 1982, will be used as a basis for this section.

According to these researchers, analysis of post-abortion fertility is difficult for a number of reasons:

- variety of abortion techniques;
- variety of conditions under which abortion is performed;
- rank of abortion (first or subsequent abortion);
- heterogeneity of women on whom abortion is performed; and
- multiple methodological biases (Table 31).

The mechanisms through which an abortion may affect a woman's subsequent fertility are, as noted in previous pages:

- cervical trauma leading to an incompetent cervix and, later, to an increased risk of miscarriage, premature delivery, or obstetric complications;
- endometrial synechias producing bleeding during pregnancy, ectopic pregnancies, or infertility; and
- PID, the healing of which causes adhesions that block the fallopian tubes.

Table 31. Definition of Comments Cited in Tables 32-37*

- 1) Follow-up under 75%
- Follow-up rate differs between exposed and unexposed, or between cases and controls
- 3) Incomplete ascertainment of outcome
- 4) Prior pregnancy history determined after outcome occurred
- Prior pregnancy history may have been determined after predisposing symptoms occurred
- 6) Prior pregnancy history determined by record review alone
- 7) Power to detect a twofold increase with $\alpha = 0.05$ is less than 0.80
- 8) Possible selection factors between cases and controls
- 9) Unsubstantiated recall of pregnancy history
- 10) Incomplete information on study and control groups
- 11) Fertility from medical records and interviews
- 12) Fertility from vital statistics and interviews
 - * The comments appear as numbers in Tables 32-37.

Source: C.J.R. Hogue, W. Cates, Jr., and C. Tietze, "The Effects of Induced Abortion on Subsequent Reproduction," *Epidemiologic Reviews* 4 (1982), 70.

Infertility

The earliest studies on this subject reported infertility rates following abortion that varied from 0 to 7.6 percent. The more in-depth and larger-scale epidemiological studies conducted later, presented in Table 32, did not demonstrate an increased infertility risk. One exception was a study carried out in Greece, where abortion was illegal, in which the risk of infertility was clearly higher for women who had undergone spontaneous and induced abortions.

Ectopic Pregnancy

The incidence of post-abortion ectopic pregnancy, in the descriptive studies, varied from 0.2 to 2 percent. The cohort studies, although limited by their small sample sizes, did not show any increased risk of ectopic pregnancy, except for one in which the risk was higher in women who had had PID or who had retained some conceptus after the abortion.

The studies reported in Table 33 show that the risk of ectopic pregnancy, if it exists, is sufficiently low to be difficult to detect in large-scale studies. The risk cannot be eliminated, however, for women who have had infectious post-abortion problems.

Spontaneous Abortion

The scientific literature on this subject reports that abortion may have a positive or negative effect on the risk of subsequent spontaneous abortions, depending on the control group used. Selected studies on this subject are listed in Table 34.

Table 32. Selected Studies of Infertility After Induced Abortion	Studies of Info	ertility After In	duced Abortion		
Study location and time (reference no.)§	Design	Abortion procedure*	Controlled variables	Comments [†]	Results
Japan, 1971 (52)	Cross- sectional	Mostly D&C	Age, duration of marriage	3, 4, 9	Gravidity was similar for those reporting and not reporting previous induced abortions
Yugoslavia, 1966-1972 (81)	Abortion	Mostly VA	Contraceptive use	1, 2, 11	Pregnancy-to-conception intervals were significantly shorter after induced abortion
Greece, 1974 (82)	Case-control	Illegal D&C	Age, parity, education	6, 8, 9	For secondary infertility >18 months, relative risk (RR) = 1.1 (0.59, 1.9)
		Illegal D&C	Age, parity, education, spontaneous abortion history	4, 8, 9	RR = 12.5 (2.3, 66.9)
Denmark, 1967-1975 (83)	Pregnancy	Mostly VA	Age, parity, socioeconomic status, regular menstrual cycle, contraceptive use	9. 4.	For pregnant women, the preceding interpregnancy interval did not significantly differ according to outcome of the preceding pregnancy
Washington, 1976-1978 (84)	Case-control	Mostly VA	Age, gravidity, race or ethnic status, marital status, socioeconomic status	4, 8, 0	For secondary infertility >12 months, RR = 1.3 (0.071, 2.4)
		Mostly VA	Age, gravidity, race or ethnic status, marital status, socioeconomic status, spontaneous	4, 8, 9	RR = 1.2 (0.41, 3.8)

	tion.	curettage: VA. vacuum aspiration.		D&C, dilatation and	*
	phic details.	source for complete bibliographic details.	le source for	Please consult table	400
impaired ability to conceive					
induced abortion had not	contraceptive use				
resulted in conclusion that	menstrual regularity,		cohort		
וב טפעפומו מוומואור וכרוווווקענט	Aye, graviaity,	Wa Kireniai	ADDITION	dii, 1970-1979 (44)	חמאם

Source: C.J.R. Hogue, W. Cates, Jr., and C. Tietze, "The Effects of Induced Abortion on Subsequent Reproduction," Epidemiologic Reviews 4 (1982), 73. The comments, presented in full and numbered in Table 31, are indicated here by number.

Study location and time (reference no.)§	Design	Abortion procedure*	Controlled variables	Comments⁺	Results
Japan, 1966 (105)	Case-control Mostly D&C	Mostly D&C	Place of residence, all multiparous	4, 6, 8, 9	Relative risk (RR) = 1.3 (0.93, 1.7)
Japan, 1958-1967 (106) Case-control [‡] Mostly D&C	Case-control*	Mostly D&C	None, all multiparous	4, 6, 8, 9	RR = 4.7 (1.8, 12.1)
Greece, 1972 (107)	Case-control	Case-control Illegal, mostly D&C	Age, gravidity, education	4, 8, 9	RR = 10.4 (2.8, 37.8)
Poland, 1973 (108)	Pregnancy cohort	Mostly D&C	All para 0	7-9	RR = 3.0 (1.0, 9.0); incidence in abortion group = 1.1%

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lable 33. (conta)					
Study location and time (reference no.) [§] Design	Design	Abortion procedure*	Controlled variables	Comments [†]	Results
Yugoslavia, 1971-1973 (109)	Case-control D&C, 73%; VA, 16% unknown, 1	D&C, 73%; VA, 16% unknown, 10%	Age	6, 8, 6	Overall, RR = 0.92 (0.62, 1.3); D&C compared with normal deliveries, RR = 1.2 (0.79, 1.8); VA compared with normal deliveries, RR = 1.5 (0.68, 3.2)
Hawaii, 1970-1979 (104)	Abortion	Mostly VA	Age, race or ethnic status, year of event	2, 3, 7	BR = 1.5 (0.77, 2.8); for abortions complicated by infection or retained products compared with all other abortions, RR = 5.0 (1.9, 12.8); incidence in abortion group = 0.64%
Boston, 1976-1978 (49)	Case-control	Case-control Illegal, VA and 13 variables D&C	13 variables	4, 8, 9	RR = 1.3 (0.6, 2.7)

Please consult table source for complete bibliographic details.

D&C, dilatation and curettage; VA, vacuum aspiration.

The comments, presented in full and numbered in Table 31, are indicated here by number.

Cases of cervical pregnancy.

Source: C.J.R. Hogue, W. Cates, Jr., and C. Tietze, "The Effects of Induced Abortion on Subsequent Reproduction," Epidemiologic Reviews 4 (1982), 75.

Table 34. Selected Studies of the Effects of Induced Abortion of the First Pregnancy on Mid-Trimester Spontaneous Abortion of the Second Pregnancy

Study location					Incidence (per 100)	Relative risk (95% confidence interval)	% confidence /al)
and time (reference no.)*	Design	Abortion procedure**	Controlled variables	Comments	in abortion group	Comparison group G2P1*	Comparison group G1 [‡]
Czechoslovakia, 1950-1960 (128)	Pregnancy cohort	Mostly D&C	None	4, 6, 8-10	2.4		3.7 (2.7, 5.2)
Debrecen, Lodz, Warsaw, 1976-1978 (64)	Pregnancy	D&C	Age, smoking, socioeconomic status, gestation at booking	ۍ ه	6.	2.7 (1.5, 5.0) 2.8 (1.5, 5.1)	2.8 (1.5, 5.1)
Helsinki, Ljubljana, Stockholm, 1976-1978 (64)	Pregnancy D&C cohort	D&C	Age, smoking, socioeconomic status, gestation at booking	5, 7, 9	1.4	2.8 (0.66, 9.4) 1.8 (0.52, 6.0)	(0.52, 6.0)
		*	Age, smoking, socioeconomic status, gestation at booking	5, 7, 9	4.	1.1 (0.22, 5.4) 0.71 (0.16, 3.1)	0.71 (0.16, 3.1)
Copenhagen, Newcastle, 1976-1978 (64)	Pregnancy	*	Age, smoking, socioeconomic status, gestation at booking	5, 7, 9	1.0	0.77 (0.22, 2.8) 0.90 (0.19, 4.3)	,90 (0.19, 4.3)
New York City, 1976-1980 (59)	Pregnancy	VA, 62%; D&C, 16%; Saline, 21%	Gestation at booking, hospital	5, 7-9	2.7	2.0 (0.53, 7.7) 0.79 (0.14, 4.5)	.79 (0.14, 4.5)

Study location					Incidence	Relative risk (95% confidence interval)	5% confidence rval)
and time (reference no.)*	Design	Abortion procedure**	Controlled variables	Comments [†]	in abortion group	Comparison group G2P1 [‡]	Comparison group G1 [‡]
Upstate New York,	Abortion cohort	D&C	Only married whites	2,3	2.3	2.7 (1.4, 5.1)	
1970-1977 (42)		*	Only married whites	, 3 9	5.9	3.4 (1.8, 6.7)	
		Saline	Only married whites	2, 3, 7	0.4	0.47 (0.07, 3.3)	
California, 1974-1976 (60)	Pregnancy cohort	Pregnancy Mostly D&C cohort (before 1973)	Age, gestation at booking	5, 6, 9	8.9		3.3 (1.7, 6.2)
		Mostly VA (after 1973)	Age, gestation at booking	5, 6, 9	3.0		1.4 (0.76, 2.7)
Hawaii, 1970-1978 (127)	Abortion	Mostly VA	Age, gestation at booking, year of event	2, 7§	5.6	0.80 (0.22, 2.9) 0.72 (0.36, 1.4)	0.72 (0.36, 1.

Please consult table source for complete bibliographic details.

D&C, dilatation and curettage; VA, vacuum aspiration.

The comments, presented in full and numbered in Table 31, are indicated here by number.

G2P1, gravidity two, parity one; G1, gravidity one. Power is <0.80 only for comparison with G2P1.

Source: C.J.R. Hogue, W. Cates, Jr., and C. Tietze, "The Effects of Induced Abortion on Subsequent Reproduction," Epidemiologic Reviews 4 (1982), 78. If pregnant women who had an induced abortion when they were pregnant for the first time (G2P0) are compared to women who are pregnant for the first time (G1), the estimated relative risk of spontaneous abortion varies from 0.71 to 3.7; the risk is higher in women who had an earlier D&C abortion (RR = 1.8-3.3) compared to women who had an earlier suction curettage abortion (RR = 0.7-1.4). When pregnant women who had an induced abortion when they were pregnant for the first time (G2P0) are compared to women who are pregnant for the second time and who gave birth the first time (G2P1), the relative risks, in particular for mid-trimester spontaneous abortion, tend to be higher (RR = 0.4-6.8). In these studies, suction curettage abortions had fewer consequences than D&C abortions. For various methodological reasons, the comparison of women who had their first pregnancy aborted (G2P0) to women who were pregnant for the first time (G1) is probably more satisfactory.

Premature Delivery

As shown in Table 35, the relative risk of premature delivery for women who have had an abortion is slightly higher when compared to that for women who have carried an earlier pregnancy to term (G2P1) rather than to that for women who are pregnant for the first time (G1P0). However, only two of these studies were able to demonstrate a significant increase in the relative risk of premature delivery in women who had previously had an abortion (Hogue et al. 1982; Franck et al. 1985).

Low Birthweight

Risk studies on low birthweight, which are often used to determine the risk of premature birth, have the same characteristics as studies on premature delivery (Hogue et al. 1982). An analysis of Table 36 shows that the risk of premature delivery in pregnant women who had an induced abortion of their first pregnancy is limited (ibid.; Franck et al. 1985).

A cohort study carried out in the United Kingdom on the risk of spontaneous abortion, premature delivery, and low birthweight following induced abortion (Franck et al. 1985) reported a relative risk of 1.24 for all these eventualities, which is not statistically significant.

Other

A definitive study of pregnancy, labour, and delivery complications in women who have had an earlier abortion is extremely difficult because different authors use different definitions and diagnostic criteria. In addition, analysis of certain complications, such as bleeding in the first trimester, is likely to be influenced by significant recall bias.

The risk of bleeding in the first trimester appears to be higher in women who have already had an abortion, according to several, but not all, studies (Hogue et al. 1982). Complications such as incompetent cervix and fibrosis uteri are reported in a contradictory fashion, without any precise trends. In general, toxaemia of pregnancy does not appear to be more frequent in women who have had an abortion.

Table 35. Selected Studies of the Effects of Induced Abortion of the First Pregnancy on Premature Delivery* of the Second Pregnancy

Study breation					Incidence	Relative risk	Relative risk (95% confidence interval)
and time (reference no.)**	Design	Abortion procedure [†]	Controlled variables	Comments*	in abortion group	Comparison group G2P1§	Comparison group G1 [§]
Debrecen, Lodz, Warsaw, 1976-1978 (64)	Pregnancy D&C cohort	D&C	Age, smoking, socioeconomic status, gestation at booking	ص	10.3	1.2 (0.84, 1.7)	1.2 (0.84, 1.7) 1.3 (0.93, 1.9)
Helsinki, Ljubljana, Stockholm, 1976-1978 (64)	Pregnancy D&C cohort	D&C	Age, smoking, socioeconomic status, gestation at booking	5, 7, 9	2.	1.2 (0.35, 4.1)	0.91 (0.30, 2.8)
		*	Age, smoking, socioeconomic status, gestation at booking	5, 7, 9	5.7	2.8 (1.3, 6.1)	1.9 (0.93, 4.1)
Copenhagen, Newcastle, 1976-1978 (64)	Pregnancy VA cohort	∀	Age, smoking, socioeconomic status, gestation at booking	5, 7, 9	4.7	1.2 (0.57, 2.6)	1.2 (0.57, 2.6) 1.0 (0.47, 2.2)
Uppsala, 1970-1978 (43)	Abortion cohort	∀	Year of event, hospital	, , ,	6.2#	1.7 (1.0, 3.1)	0.97 (0.57, 1.6)

			The Impact	of Medical Pro	ocedures on Fertil
0.72 (0.38, 1.4)	1.1 (0.87, 1.3)¶ 0.75 (0.29, 1.9)	0.75 (0.28, 2.0)	1.3 (0.91, 1.8)	1.1 (0.50, 2.3)	0.74 (0.08, 6.9)
1.0 (0.56, 2.1)	(0.87, 1.3)¶	1.1 (0.46, 2.6)	1.7 (1.1, 2.6)	1.6 (0.93, 2.6)	1.0 (0.93, 1.1)
1.0	=	臣	1.7	5.	0.1
φ. 8.	1.6	1.6	დ <i>G</i>	φ	9.00
ი ,	N	2,7	, v,	5, 7, 9	5, 7, 9
Race or ethnic status, socioeconomic status	Age, race or ethnic status (white), education, place of residence, marital status	Age, race or ethnic status (white), education, place of residence, marital status	Age, race or ethnic status (white), education, place of residence, marital status	Age, race or ethnic status, gestation at booking	Age, race or ethnic status, gestation at booking
Not given	D&C	۸ ۷	Saline	<14 weeks' gestation	≥14 weeks' gestation
Pregnancy Not given cohort	Abortion			Pregnancy cohort	
Boston, 1975-1976 (62)	Upstate New York, 1970-1977 (42)			New York City, 1976-1980 (59)	

Comparison group G1 [§]	0.96 (0.56, 1.6)	0.57 (0.23, 0.90)
Comparison group G2P1 [§]		1.4 (0.40, 2.4)
(per 100) - in abortion group	6.	3.8
Comments	4, 5, 9	2, 3, 6
Controlled variables	Age, religion, marital status, socioeconomic status	Age, race or ethnic status, year of event
Abortion procedure [†]	Mostly VA	Mostly VA
Design	Pregnancy	Abortion
Study location and time (reference no.)**	Seattle, 1972-1976 (151)	Hawaii, 1970-1978 (44)
	Abortion Controlled in abortion Comparison (" Design procedure variables Comments group group G2P1§	Abortion Controlled in abortion Comparison procedure variables Comments group G2P1s Pregnancy Mostly VA Age, religion, 4, 5, 9 9.2 cohort socioeconomic status, status

<37 or 38 weeks' gestation (except for reference 42, which is <33 weeks' gestation).</p>

Please consult table source for complete bibliographic details.

D&C, dilatation and curettage; VA, vacuum aspiration.

The comments, presented in full and numbered in Table 31, are indicated here by number.

G2P1, gravidity two, parity one; G1, gravidity one.

Power is <0.80 only for comparison with G2P1.

Point estimate and confidence intervals calculated for this review vary slightly from those in original report.

Variables were controlled through matching of cohorts; therefore, cohorts differ somewhat

Source: C.J.R. Hogue, W. Cates, Jr., and C. Tietze, "The Effects of Induced Abortion on Subsequent Reproduction," Epidemiologic Reviews 4 (1982), 79.

Table 36. Selected Studies of the Effects of Induced Abortion of the First Pregnancy on Low Birth Weight* in the Second Pregnancy

Study location					Incidence	Relative risk (95% confidence interval)	5% confidence val)
and time (reference no.)**	Design	Abortion procedure [†]	Controlled variables	Comments*	in abortion group	Comparison group G2P1§	Comparison group G1 [§]
Budapest, 1962 (77)	Pregnancy cohort	D&C	Age	4, 8, 9	12.8		1.4 (1.2, 1.5)
Hungary, 1970-1971 (152)	Pregnancy cohort	D&C	None	4", 8, 9	13.6	1.6 (1.4, 1.9)	1.5 (1.3, 1.7)
Debrecen, Lodz, Warsaw, 1976-1978 (64)	Pregnancy cohort	D&C	Age, height of mother, socioeconomic status, smoking	6 'S	9 2	1.6 (1.1, 3.3)	1.2 (0.83, 1.6)
Japan, 1962 (156)	Pregnancy cohort	Mostly D&C None	None	5, 8-10	4.6		1.1 (0.66, 1.9)
Japan, 1971 (124)	Cross- sectional	Mostly D&C None	None	3, 4, 7-91	13.8	2.0 (1.2, 3.5)	1.5 (0.88, 2.4)
Singapore, 1974-1977 (46)	Abortion	VA, 75%; D&C, 25%	Race or ethnic status (Chinese), socio- economic status (poor)	2, 7, 8	18.5	2.7 (1.3, 5.5)	1.4 (0.74, 2.6)

					Incidence	Relative risk int	Relative risk (95% confidence interval)
Study location and time (reference no.)** Design	Design	Abortion procedure [†]	Controlled variables	Comments [‡]	in abortion group	Comparison group G2P1 [§]	Comparison group G1 [§]
Helsinki, Ljubljana, Stockholm, 1976-1978 (64)	Pregnancy cohort	D&C	Age, height of mother, socioeconomic status, smoking	5, 71, 9	6:1	0.61 (0.17, 2.2)	0.51 (0.15, 1.8)
		*	Age, height of mother, socioeconomic status, smoking	5, 7, 9	5.2	1.6 (0.73, 3.4)	1.2 (0.58, 2.6)
Skopje, 1968-1972 (65)	Abortion	Mostly VA	Socioeconomic status	1, 2, 7	5.6		1.5 (0.50, 2.6)
Rostock, 1969-1977 (158)	Pregnancy cohort	Not given	None	4", 6, 8, 9	10.7		1.9 (1.4, 2.7)
Magdeburg, 1973-1976 (115)	Pregnancy cohort	Mostly VA	None	4, 6, 8, 9	6.7		1.2 (0.70, 2.0) ⁺⁺
Zwickau, 1977-1979 (123)	Pregnancy cohort	Mostly VA	None	5, 8, 9	7.4		1.2 (0.76, 1.9)
Copenhagen, 1967-1973 (147)	Pregnancy cohort	Mostly VA	Age	5, 6, 8, 9	8.9	0.60 (0.31, 1.2)	0.60 (0.31, 1.2) 0.80 (0.39, 1.6)
Copenhagen, Newcastle, 1976-1978 (64)	Pregnancy cohort	۸۸	Age, height of mother, socioeconomic status, smoking	5, 7, 9	6.1	1.1 (0.55, 7.0)	1.3 (0.64, 2.5)

					The	Impact of Me	dical Procedures
1):: (:):))	1.1 (0.46, 2.7)** 1.7 (0.62, 4.5)**	1.2 (0.67, 2.0)** 0.83 (0.49, 1.4)**	0.90 (0.21, 3.8)# 0.77 (0.41, 1.4)#	1.4 (1.0, 1.9)#	1.3 (0.86, 2.1)** 1.2 (0.80, 1.8)**	0.99 (0.82, 1.2)	0.96 (0.54, 1.7)
		1.2 (0.67, 2.0)**	0.90 (0.21, 3.8)#	1.6 (1.1, 2.3)#	1.3 (0.86, 2.1)**	1.7 (1.0, 2.8)	1.8 (0.72, 4.5)
1	6.	6.8	5.2	8.6	7.5	7.1	6.7
	5, 6, 7-9	ري م	α	α	N	5, 7¶, 9	5, 71, 9
	Age, race or ethnic status, marital status, socioeconomic status, place of residence	Race, socioeconomic status	Age, race or ethnic status (white), marital status	Age, race or ethnic status (white), marital status	Age, race or ethnic status (white), marital status	Age, race or ethnic status, height of mother, smoking, sex of infant	Age, race or ethnic status, height of mother, smoking, sex of infant
	D&C or VA	Not given	D&C	*	Saline	<14 weeks' gestation	≥14 weeks' gestation
	Pregnancy	Pregnancy Not given cohort	Abortion			Pregnancy	
(21) 2121 2121	Baltimore, 1971-1977 (58)	Boston, 1975-1976 (62)	Upstate New York, 1970-1977 (42)			New York City, 1976-1980 (59)	

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					Incidence	Relative risk (9	Relative risk (95% confidence interval)
and time (reference no.)** Design	Design	Abortion Controlled procedure [†] variables	7	Comments [‡]	abortion	abortion Comparison Comparison group G2P1 [§] group G1 [§]	Comparison group G1 [§]
Seattle, Pregna 1972-1976 (151) cohort	Pregnancy cohort	Mostly VA	Pregnancy Mostly VA Age, race or ethnic schort status, marital status, socioeconomic status, religion	4, 5, 9	6.0		0.88 (0.45, 1.7)
Hawaii, 1970-1978 (44)	Abortion	Mostly VA	Age, race or ethnic status, year of event	2, 3, 6	4.955 1	4.9 ^{§§} 1.1 (0.23, 1.9)	0.90 (0.33, 1.5)

* <2 500 or 2 501 g (except for reference 58, which is <1 501 g).

** Please consult table source for complete bibliographic details.

D&C, dilatation and curettage; VA, vacuum aspiration.

The comments, presented in full and numbered in Table 31, are indicated here by number.

G2P1, gravidity two, parity one; G1, gravidity one.

Prior pregnancy history may have been determined after outcome occurred.

Power <0.80 only for G2P1 comparison.

Control group includes some with previous experience of spontaneous abortion.

Point estimates and confidence intervals calculated for this review vary slightly from those in original report. # 85

Source: C.J.R. Hogue, W. Cates, Jr., and C. Tietze, "The Effects of Induced Abortion on Subsequent Reproduction," Variables were controlled through matching of cohorts; therefore, cohorts differ somewhat.

Epidemiologic Reviews 4 (1982), 82-83.

With respect to complications during labour or delivery, none of the more rigorous studies reported any increased risk when women who had had an abortion (G2PO) were compared to those who were pregnant for the first time (G1) (Hogue et al. 1982). An increased risk was found in a number of studies when women who had had an abortion (G2PO) were compared to those in their second pregnancy who had already given birth to a child (G2P1).

In most of the studies, with only a few exceptions, infant mortality and morbidity do not appear to be affected by the fact that a woman has had a prior abortion (Hogue et al. 1982).

Impact of Repeated Abortions on Fertility

In the literature review mentioned earlier, 13 studies made it possible to analyze the effects of repeated abortions on subsequent fertility. The results of these studies are given in Table 37.

Two studies reported conflicting and not statistically significant results concerning ectopic pregnancy. There is an association between repeated abortions and the risk of subsequent spontaneous abortion, but the studies in question were done on D&C abortions and not suction curettage abortions (Hogue et al. 1982).

No association between induced abortion and subsequent premature delivery was found (Hogue et al. 1982; Lopes et al. 1991), except in one study in which the risk of premature delivery appeared to be linked more to considerable cervical dilatation than to the number of abortions (Hogue et al. 1982).

There are also conflicting results concerning the association between the number of abortions and low birthweight (Hogue et al. 1982; Lopes et al. 1991). Once again, the D&C technique would appear to be involved.

It would be worth doing further research on the impact of repeated abortions on subsequent fertility, taking into consideration the type of technique used to perform the abortions, as well as the many potentially confounding variables.

To summarize, it would not appear that having had an induced abortion significantly increases the risk of infertility or of complications in a subsequent pregnancy, either for the mother or for the child. However, beyond the minimal risk of a hysterectomy following an abortion, complications such as PID or endometrial synechias can lead to infertility in a small proportion of women. The risk is extremely low when preventive measures are taken, when the doctors performing the abortions are experienced, and when complications are treated quickly and properly. However incomplete it may be, the scientific literature is reassuring with respect to the impact of repeated abortions on fertility.

Abortion	Controlled	Comments	Outcome	Results
Pregnancy D&C cohort		4, 6°, 8, 9	Low birth weight	For 2 abortions compared with G2P0, relative risk (RR) = 1.6 (1.4, 1.9); for 3 abortions compared with G2P0, RR = 1.8 (1.5, 2.1)
Pregnancy D&C cohort	None	4, 6 ⁵ , 8, 9	Low birth weight	For 2 abortions compared with G2P0, RR = 1.5 (1.0, 2.3); for 3 abortions compared with G2P0, RR = 1.7 (1.0, 3.1)
Pregnancy D&C cohort	None	4, 6, 8, 9	Low birth weight	Compared with G2P1, RR = 2.1 (1.6, 2.6); compared with G1, RR = 1.7 (1.3, 2.1)
Pregnancy D&C cohort	Age, gravidity, spontaneous abortion history, socioeconomic status	5, 6, 9	Mean birth weight and mean gestation	No increased risk of either
Cross- D&C sectional	Age	3, 4, 8, 9	Spontaneous abortion	RR = 1.5 (1.2, 1.9)
Pregnancy D&C and V cohort	A None	5, 7-9	Low birth weight	Compared with G2P0, RR = 1.7 (0.8, 3.5)
S- on on	al ncy	D&C al ncy D&C and VA	status D&C Age al ncy D&C and VA None	status D&C Age 3, 4, 8, 9 al ncy D&C and VA None 5, 7-9

a'							
חח = ו.ב (ט.ס, ו.ש)	RR = 1.5 (0.7, 3.1)	No significant increase in risk	Compared with G2P0, RR = 0.87 (0.27, 2.8)	Compared with G2P0, RR = 1.1 (0.44, 2.7)	No increased risk of either	RR = $2.1 (p < 0.01)$	Compared with G2P1, RR = 2.6 (1.2, 6.0); compared with G1, RR = 1.9 (0.73, 4.9)
during during pregnancy	Retention of placenta	Mean birth weight	Low birth weight	Shortened gestation	Mean birth weight and mean gestation	Spontaneous abortion	Low birth weight
ກ ່ຕໍ່ ດໍ	5, 7-9	5, 7, 9	5, 7, 9	5, 7, 9	5-9	4, 8, 9	5, 7, 9
IVOILE	None	Age, spontaneous abortion history, sex of infant, gestational age, marital status, smoking	None	None	Age, gravidity, spontaneous abortion history, socioeconomic status	26 variables	Age, race or ethnic status, gestation at booking, height of mother, smoking, sex of infant
D&C and vA	D&C and VA	∀	۸×	۸ ۸	Mostly VA	Case-control Legal, mostly VA	VA and D&C
		Abortion			Pregnancy cohort	Case-control	Pregnancy cohort
		Uppsala, 1970-1978 (43)			Seattle, 1972-1976 (101)	Boston, 1976-1978 (37)	New York City, 1976-1980 (59)

Study location and time (reference no.)**	Design	Abortion procedure [†]	Controlled variables	Comments	Outcome studied	Results
New York City, 1976-1980 (59) (cont'd)		VA and D&C	Age, race or ethnic status, gestation at booking, height of mother, smoking, sex of infant	5, 7, 9	Shortened	Compared with G2P1, RR = 1.5 (0.36, 6.2); compared with G1, RR = 1.4 (0.31, 5.9)
		VA and D&C	Age, race or ethnic status, gestation at booking, height of mother, smoking, sex of infant	5, 7, 9	Тохетіа	Compared with G2P1, RR = 4.2 (1.5, 11.4); compared with G1, RR = 1.5 (0.19, 2.3)
		VA and D&C	Age, race or ethnic status, gestation at booking, height of mother, smoking, sex of infant	5, 7, 9	Premature rupture of the membranes	Compared with G2P1, RR = 1.7 (0.81, 3.6); compared with G1, RR = 1.0 (0.88, 1.2)
California, 1974-1976 (60)	Pregnancy	Mostly VA (after 1973)	Age, gestation at booking	6-7, 9	Spontaneous	For second-trimester spontaneous abortion compared with G1, RR = 3.1 (1.6, 6.2)
Hawaii, 1970-1978 Abortion (44)	3 Abortion cohort	Mostly VA	None	2, 3, 7	Ectopic pregnancy	Compared with 1 prior abortion, RR = 0.94
	н	Mostly VA	Multivariate confounder score including parity	2, 3, 7	Spontaneous	Compared with no prior abortion, RR = 1.01 for first-trimester spontaneous abortion; RR = 0.80 for second-

abortion	Compared with no prior abortion, RR = 0.86	Compared with no prior abortion, RR = 1.00	Compared with no prior abortion, RR = 0.91	Compared with no prior abortion, RR = 0.94	Compared with no prior abortion, RR = 1.44	Compared with no prior abortion, RR = 1.03	RR = 2.6 (0.9, 7.4)
	Low birth weight	Shortened gestation	Pregnancy complications	Labor complications	Congenital malformations	Postneonatal death	Ectopic
	2, 3, 7	2, 3, 7	2, 3, 7	2, 3, 7	2, 3, 7	2, 3, 7	4, 7-9
	Multivariate confounder score including parity	15 variables					
	Mostly VA	Case-control Illegal, VA and 15 variables D&C					
							Boston, 1976-1978 (49)

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Multiple abortions are classified as 2 or more, unless otherwise noted

Please consult table source for complete bibliographic details.

D&C, dilatation and curettage; VA, vacuum aspiration.

The comments, presented in full and numbered in Table 31, are indicated here by number. Prior pregnancy history may have been determined by record review alone.

Prior pregnancy may have been determined after outcome occurred.

Source: C.J.R. Hogue, W. Cates, Jr., and C. Tietze, "The Effects of Induced Abortion on Subsequent Reproduction," Epidemiologic Reviews 4 (1982), 86-87.

Urological Procedures

Urological procedures refer to surgery on the male genital organs and their accessory organs (perineal ganglia, etc.).

Urological procedures involving resection of the bladder neck or the prostate may lead to male infertility through retrograde ejaculation (Whitmore and Morse 1986). Following radical prostatectomy, impotence occurs in 60 to 90 percent of cases (Finkle and Taylor 1981; Whitmore and Morse 1986). In 1983, Walsh et al. developed a modification of the prostatectomy procedure that preserved sexual function in most cases.

According to the literature review by Lange et al. (1987), most men with testicular cancer have lowered fertility. However, according to these authors, it is not clear whether this state is temporary or permanent. One way to treat testicular cancer involves removal of the affected testicle and, if required, a retroperineal lymphadenectomy. According to the publications reviewed, many men who undergo the retroperineal lymphadenectomy become infertile (Orecklin et al. 1973; Skinner 1976; Kedia et al. 1977; Whitmore and Morse 1986; Lange et al. 1987; Lange and Brawer 1990). The surgery in fact causes lesions in the sympathetic nervous system, which plays a role in ejaculation (Lange et al. 1987). A recent modification to the surgical procedure (unilateral dissection) makes it possible to preserve ejaculation in 75 to 90 percent of cases without compromising cancer treatment (ibid.; Lange and Brawer 1990).

Inquinal Hernioplasty

Inguinal hernioplasty consists of reducing a protruding hernia in the

inguinal region.

Testicular atrophy caused by ischaemia may be encountered after inguinal hernioplasty. This complication occurs in less than one case per 1 000 (Wantz 1982, 1986). The incidence may increase to 5 percent if surgery is required again for a recurrence (Wantz 1982). Various authors report that, in spite of these complications, subsequent fertility appears to remain unchanged (ibid.; Pollak and Nyhus 1983). However, we did not find any papers discussing this problem.

Acute Appendicitis in Women

Recent publications on infertility following acute appendicitis are few in number. The literature review of this subject will therefore refer

primarily to data reported in the 1960s and 1970s.

The English author Powley (1965) and the American author Thompson (1971) reported that infertility problems were more frequent following pelvic abscess and pelvic peritonitis in acute appendicitis than following acute appendicitis without complications. It is important to note, however, that the number of cases analyzed by Thompson was very small (six).

Geerdsen and Hansen (1977) in Denmark and Wiig et al. (1979) in Norway wrote that acute appendicitis without complications did not affect fertility potential, but that fertility could be slightly decreased in the presence of complications.

Several of the authors cited above appear to agree that, where signs and symptoms suggest appendicitis in young women, early diagnosis and treatment are in order, to preserve fertility potential (Thompson 1971; Geerdsen and Hansen 1977; Trimbos-Kemper et al. 1982).

Radiation Therapy

This section considers the impact of radiation therapy on male and female reproductive organs.

Radiation therapy is used to treat various forms of cancer (lymphoma, Hodgkin's disease, etc.). Women's ovaries are very sensitive to radiation therapy, which destroys reproductive cells. The ovaries become increasingly sensitive as a woman becomes older (Mettler and Moseley 1985). In fact, following radiation therapy, women under 30 years of age retain their reproductive function and menstruation more often than women over 30 years of age (Mitchell et al. 1991). Abdominopelvic treatment exposes the ovaries to approximately 1 200 to 5 000 rads of radiation. A single dose of 150 to 650 rads or partial doses totalling 150 to 1 200 rads temporarily reduce fertility (Moss and Brand 1969; Mitchell et al. 1991). Permanent infertility, however, may occur after a single dose of 320 to 1 000 rads (Mettler and Moseley 1985; Mitchell et al. 1991).

In men, pelvic radiation therapy is used to treat cancer of the prostate, the bladder, and the colon. Typically, men with cancer of the prostate are exposed to 5 000 rads in the pelvic area and 2 000 rads in the prostate area. A temporary decrease in the sperm count is reported after an irradiation of 15 rads, and aspermia is reported after 50 rads. After treatment of 200 to 300 rads, sperm production recovers completely within one to three years (Sherins and Howards 1986). Permanent sterility appears after treatment of over 600 rads (DeKernian 1976; Sherins and Howards 1986). An incidence of impotence of 22 to 84 percent was reported following radiation therapy for cancer of the prostate (Sherins and Howards 1986).

In summary, radiation therapy has a harmful effect on the fertility of those who undergo it. The effect is stronger as the radiation increases. The quantity of radiation required is nevertheless determined by the severity of the disease treated in this way.

Discussion and Recommendations

This review of the literature on infertility as a result of medical procedures discussed a large number of surgical procedures and diagnostic tests that could directly or indirectly have an impact on human fertility. An exhaustive search of the medical literature was carried out and several

studies on the short- and long-term complications of procedures and tests were surveyed. These yielded relevant information on the probability of infertility following these procedures and tests.

To summarize, it was found that voluntary sterilization procedures are very much in demand and widely performed in Canada, for both women and men. The negative impact of these procedures is primarily related to the regret felt by a number of individuals, and to the fact that some among them eventually request a reversal of the procedure. Although regret following sterilization is reasonably well documented for women, little is known on this matter regarding men. Some approaches that might reduce the impact of such procedures on fertility include identifying those individuals who show risk factors and are all the more likely to experience regret, as well as developing new contraceptive methods and practising sterilization techniques that have a minimal effect on anatomical structures.

The frequency of hysterectomies has been in constant decline for 20 years, but they are being performed in greater numbers on older women. The exact reasons for the decline in the incidence of hysterectomies are not known. A number of hypotheses may be put forward, notably the introduction of alternative therapies to hysterectomy, a change in the behaviour of surgeons with respect to the indications for such procedures, increased control by women over their own bodies, preventive screening leading to early therapy for a number of pathologies, and the use of oral contraceptives that decrease the incidence of a number of gynaecological cancers.

Several therapeutic approaches make it possible to delay or prevent hysterectomies, but their impact on decreasing the hysterectomy rate is not documented. Some of these alternative therapies are also in the experimental stage and need further study before general conclusions can be drawn.

For surgery or diagnostic tests that have an indirect impact on fertility, it was extremely difficult to collect enough information to draw firm conclusions. The prenatal tests described in this report were studied extensively; nevertheless, apart from the risk of spontaneous abortion, the other potential complications were barely identified or not identified at all, or quantified, in the literature. For example, there is no information about the risk of infertility for women who had a spontaneous abortion complicated by endometritis. The scarcity of this occurrence makes it difficult to do a specific analysis of it.

Little is known about the impact on fertility of diagnostic or therapeutic procedures used to check an infertile couple, such as hysterosalpingography, endometrial biopsy, hysteroscopy, laparoscopy, vasography, and testicular biopsy. Nevertheless, the risk of infection related to these techniques has been studied in several publications. Of all these procedures, hysterosalpingography is the most widely studied: it has been shown that the risk of infection following its use is low, and hence the

risk of subsequent infertility is even lower. The same can be said for laparoscopy. As for the potential complications attendant upon endometrial biopsy and hysteroscopy, they are barely quantified at all in the literature. In men, diagnostic tests and their complications have not been documented extensively; nevertheless, the procedures seem justified by the fact that microsurgery of the vas deferens has proved to be a successful avenue of therapy.

The impact of Caesarians and other instrumental procedures used in delivery on fertility was examined. Of the complications reported, only women with pelvic abscess are susceptible to having their subsequent fertility diminished. Other reasons to explain any possible decrease in fertility have not been documented.

Intrauterine devices and induced abortion are certainly the best known and most studied techniques in terms of complications and their impact on fertility in all the scientific literature concerning gynaecological surgical techniques. It is important to acknowledge that the facts show that the IUDs currently available in Canada are not in themselves infertility risk factors. However, their use in women who are at risk for PID and infertility potentiates these phenomena. It is therefore extremely important that the IUD be used only for monogamous women, and that it be associated with early and effective detection and treatment of STDs.

The data indicate that induced abortion has a minimal impact on subsequent fertility. A legal abortion, performed in well-equipped facilities by properly trained doctors, can be considered minor surgery. However, it must not be forgotten that the risk of complications, while very low, increases with the length of gestation and the intrusiveness of the technique used. Early detection of pregnancy, availability of services, use of less invasive techniques, and a number of preventive measures could effectively diminish the complications of induced abortion and reduce to zero the risk of such a procedure to fertility. The small number of studies done on repeated abortions does not allow us to be as definite concerning their impact on subsequent fertility. Although reassuring, these studies would benefit from new corroborating data.

We note in passing that studies carried out in the 1960s and 1970s on cervical surgery do not allow us to draw firm conclusions with respect to their impact on fertility. On the other hand, surgery for urological pathologies has an extremely serious impact on male fertility; alternative therapies that would retain subsequent fertility are currently being explored. Surgery affecting organs other than the reproductive organs appears to have a limited impact on fertility, but is not very well documented.

This brief survey of the contents of our literature review enables us to state that studies on the causal links between surgical procedures and diagnostic tests on the one hand and infertility on the other are rather rare. The problems encountered in collecting such studies have caused this literature review to become a survey of the complications arising in surgical

procedures and other tests. The small number of recent studies on these subjects (after 1980) has forced us to refer to older studies. Curiously, the use of IUDs and induced abortion, which result primarily from the personal decisions of the patients, are the only techniques that have been studied frequently and in depth. The other procedures and tests, over which doctors have nearly exclusive control, are not so well documented.

Methodologically speaking, studying these complications is also a In fact, the study of short- and long-term complex undertaking. complications following medical procedures depends on many factors. Prospective analyses can be carried out for short-term complications provided that the number of procedures is high enough for study, that the follow-up period is short, that individuals are followed up thoroughly, and that there is satisfactory control over confounding factors. However, from both practical and financial standpoints, it is often impossible to meet these basic requirements. Analyzing long-term complications, which is usually done through case-control studies, is even more difficult, because it is subject to important practical problems and numerous methodological biases. Moreover, many surgical procedures surveyed are performed on a population already considered infertile. How, then, to determine the degree of infertility caused by the procedures used? How is it possible to identify their impact where the infertility is joint or idiopathic? Lastly, the treatment of complications arising from the procedures has improved considerably, particularly with respect to infectious complications — so much so, in fact, that the impact of certain complications depends not only on the type of complication observed but also on the treatment used for it.

It is worth noting that the purpose of many of the procedures is diagnostic or therapeutic, and that their advantages may outweigh their disadvantages. For example, due consideration must be given to the impact of prenatal tests on subsequent fertility; however, due consideration must also be given to the value of the information sought in view of the diagnostic reliability of such tests and their risks. Precise indications, like those set forth by the CCMG and the SOGC, make it possible to cope with such problems and place the techniques in question within an acceptable ethical framework. The same is true for procedures such as hysterectomies and prostatectomies, which have precise pathological indications but permanent consequences for fertility.

Certain recommendations may therefore be made that might steer the issue toward new avenues:

1. Ethically, it appears important that such procedures and tests be used in accordance with precise indications or guidelines. Such indications or guidelines, formulated by experts, have the advantage of making it easier for doctors to perform their medical procedures. They also place limits on the overly permissive use of certain techniques. Also, the introduction of an evaluation process that uses objective criteria to outline complications for

procedures and tests, within the framework of medical procedure evaluation committees, makes it possible to detect risk factors for complications and to open new avenues for research. Lastly, an awareness of a number of preventive practices (screening, prophylactic antibiotic therapy), appropriate treatment of complications, and the development of the technical skills needed to perform the surgery and diagnostic tests in question should play a leading role in the training of doctors working in areas related to human reproduction.

- 2. *In research*, many issues have not yet been analyzed or could be updated:
 - incidence of post-vasectomy regret and risk factors;
 - evaluation of the effectiveness and safety of new contraceptive methods and less invasive and more readily tolerated sterilization methods;
 - impact of alternative treatments on hysterectomy;
 - regular updates of diagnoses indicating hysterectomy;
 - study of the short-term complications of hysteroscopy, endometrial biopsy, testicular biopsy, etc.;
 - study of the long-term complications resulting from cervical surgery and repeated induced abortions; and
 - study of the psychosocial factors that may affect fertility following a Caesarian or an instrumental delivery.
- 3. From the public information standpoint, it would be useful to develop tools to inform people about the benefits and disadvantages of surgery and diagnostic tests. Notions on the impact of such procedures on fertility should be included in this type of information and discussed with the women and men when their consent is being obtained to perform such a procedure. We cannot emphasize enough how important informed consent is in the practice of medicine, particularly when the procedures being performed affect an area as sensitive as human reproduction.

Conclusion

The Royal Commission on New Reproductive Technologies wanted to clarify the possible relationships between previous medical procedures and infertility. This review of the literature on infertility resulting from medical procedures has allowed us to see that there are few specific studies of the subject, although some studies bearing on the complications of such procedures partly clarify these relationships.

Beyond the procedures that have a direct impact on fertility, it is extremely difficult to establish a causal link between therapeutic surgery and diagnostic tests and human infertility. We cannot, however, overlook the complications of such procedures, which may in certain circumstances have a negative impact on fertility. The frequency of such complications is often poorly documented, and the data in this respect are often contradictory and of little significance.

A decrease in the incidence of hysterectomies in Canada was also noted, as well as the development of alternative and less invasive therapies for the treatment of gynaecological and urological pathologies. A concern to prevent complications from surgical procedures has also been more in evidence lately in the medical literature.

The development of precise protocols and indications for the use of surgical procedures and other tests would appear to be a concrete, short-term avenue for providing guidance to the medical profession. The development of research procedures to study the complications of such surgery and other related subjects is another solution, but a longer-term one. Lastly, the implementation of informed consent appears to us to be the most pressing recommendation, because it would allow each individual to make his or her own decisions, and confer upon doctors the responsibility not only to care but to inform.

Glossary

Adhesion: abnormal, congenital, or cicatricial union of two adjoining surfaces normally independent.

Adnexa: appendages to the uterus: the ovaries and the fallopian tubes.

Alpha-fetoprotein: type of protein produced during fetal life.

Amniocentesis: puncture of the uterus of a pregnant woman, in order to remove amniotic fluid.

Amniotic: relating to the amnios, the innermost membrane enclosing the fetus.

Anaesthesia: total or partial loss of sensation or of consciousness.

Anovulation: absence of ovulation, the production of ova by the ovary.

Anti-progesterone: chemical that blocks the production of progesterone.

Appendectomy: surgical removal of the appendix.

Artificial insemination: introduction of sperm into the female genital tract. **Asherman's syndrome**: amenorrhoea caused by uterine adhesions resulting from trauma (curettage).

Atrophy: reduction in size of an organ.

Azoospermia: absence of spermatozoa in the semen.

Biopsy: removal of pieces of tissue for microscopic examination.

Bladder neck: part of the bladder.

Caesarian section: an incision in the uterus to deliver the fetus.

Castration: surgical removal of reproductive glands.

Cellulitis: inflammation of cellular tissue, which can occur wherever cellular tissue is found, but typically involves subcutaneous regions.

Cerclage of the cervix: the encircling of the cervix to prevent dilatation.

Cervical: relating to the cervix.

Cholecystectomy: surgical removal of the gallbladder.

Cholelithiasis: presence of gallstones in the gallbladder or biliary ducts.

Chorioamnionitis: infection of the chorion and the amnios (fetal membranes).

Chorion: tissue that surrounds the embryo during the first two months.

Chorionic: relating to the chorion.

Chromosomal translocation: structural abnormality of the chromosomes, causing certain diseases.

Chromosome: element of the cell: it carries the genes that convey hereditary characteristics.

Clip: surgical fastener. **Coital**: relating to coitus.

Colposcopy: examination of the cervix with a strong magnifying lens.

Congenital: present in the individual at the time of birth (not to be confused with "hereditary").

Conization: removal of a cone-shaped part of the cervix.

Contraception: temporary and reversible methods aiming to prevent fertilization. **Curettage**: process of removing, with a curette, morbid or unhealthy tissues from the walls of a natural (uterus) or pathological (abscess) cavity.

Diethylstilbestrol: synthetic hormone.

Dilatation: enlarging the opening of an organ.

Dilatation-curettage (D&C): dilating the cervix and removing uterine contents with a curette.

Dilatation-evacuation-curettage: dilating the cervix, removing the conceptus with forceps, and removing other uterine contents with a curette.

Dilator (Pratt, Hegar): types of devices used for dilatation.

DNA: deoxyribonucleic acid. **Doxycycline**: antibiotic.

Durhssen incision: incision to the cervix performed during a delivery.

Dysfunctional: problems with an organ that seem due not to a lesion, but to abnormal functioning.

Dysmenorrhoea: difficult and painful menstruation.

Echography: exploration of a body organ or area using ultrasounds.

Ectopic: located away from its normal site.

Electro-coagulation: modifying tissues with a high-frequency electric current. **Embolism**: the sudden occlusion of a blood vessel by a blood clot or any foreign object carried in the bloodstream.

Embryo: name given to the conceptus during the first two months of gestation.

Endomectomy: surgical removal of the uterine endometrium.

Endometriosis: the growth of endometrial tissue in abnormal locations, which can cause pain and infertility.

Endometritis: inflammation of the endometrium.

Endometrium: the mucous membrane lining the uterus.

Endoscopy: technique allowing visual inspection of an internal cavity of the body.

Fallope ring: ring-shaped device used to block the fallopian tubes.

Fascia: tissue enclosing muscles or organs.

Fertility: capacity of a living being to reproduce. **Fibrosis**: degeneration of an organ into fibrous tissue.

Forceps: instrument shaped like salad tongs, ending with large spoons, and used

to pull the fetus's head during delivery.

Gastrointestinal: relating to the stomach and the intestines.

Genetics: the study of heredity.

Gestation: the period during which a woman carries the fetus.

Gonadal: relating to the gonads.

Haematoma: effusion of blood in a tissue.

Haemorrhage: escape of a quantity of blood from a blood vessel.

Hernioplasty: surgical repair of a hernia.

Histologic: relating to the part of biology that studies the formation, evolution, and composition of tissues.

Hodgkin's disease: disease of the lymphatic system.

Hyperplasia: abnormal growth of a qualitatively normal anatomic element.

Hysterectomy: partial or total removal of the uterus.

Hysterosalpingography: radiographic examination of the uterus and fallopian tubes.

Hysteroscopy: technique allowing visual examination of the uterine cavity.

Hysterotomy: incision in the uterus. **Idiopathic**: having no known cause.

Immunological: relating to immunity and its consequences.

Incompetent cervix: dilatation of the cervix before the end of the pregnancy.

Induced abortion: voluntary interruption of pregnancy.

In utero: describes phenomena affecting the embryo or fetus in the uterus.

Ischaemia: lack of blood supply in a part of an organ.

IUD: intrauterine device: a contraceptive device made of plastic or metal or both, inserted in the uterus.

IVFET: in vitro fertilization and embryo transfer.

Karyotype: chromosomal analysis.

Laminaria: pieces of dried algae or synthetic material that swell when wet and are used to dilate the cervix.

Laparoscopy: endoscopic examination of the abdominal cavity.

Laparotomy: surgical incision into the abdomen. **Leiomyoma**: tumour consisting of muscular tissue.

Leucorrhoea: whitish discharge from the vagina and the uterine cavity.

LH-RH agonist: hormonal treatment.

Luteal: relating to the ovary.

Lymph nodes: small masses found along the course of the lymphatic vessels.

Lymphodenectomy: surgical removal of a lymphatic area.

Lymphoma: disease of the lymphatic system.

Medullar (tube): relating to the spinal cord.

Menometrorrhagia: excessive menstrual flow.

Micro-organism: bacteria. **Morbidity**: relating to disease.

Mucus: substance secreted by mucous membranes.

Neural (tube): relating to the nervous system of the embryo.

Orchidectomy: surgical removal of one or both testes.

Osteoporosis: reduction in bone tissue.

Ovariectomy: surgical removal of one or both ovaries.

Ovulation: production of ova by the ovaries.

Pelvic: relating to the pelvis.

Pelvic inflammatory disease (PID): inflammation of the uterus and the fallopian

Penectomy: surgical removal of the penis.

Perineal: relating to the area between the anus and external genital organs. **Peritoneal**: relating to the peritoneum, the membrane that lines the abdomen.

Peritonitis: infection of the peritoneum (abdominal cavity).

Placenta: organ that connects the embryo to the uterus during pregnancy.

Pneumoperitoneum: the presence of gas in the abdomen.

Polyp: pedunculated mass.

Premature birth: birth before the full term of gestation.

Primipara: woman giving birth for the first time. **Progesterone**: hormone secreted by the ovary.

Prolapsus: the falling of an organ following the weakening of its retaining system. **Prophylactic**: relating to prophylaxis (means taken to prevent the occurrence or propagation of a disease).

Prophylactic antibiotic therapy: use of antibiotics to prevent the occurrence or

propagation of an infection.

Prostaglandins: hormones found in many tissues and organs, and whose different types have a wide range of biochemical actions (they play a role in most reproductive processes; in particular, they stimulate the dilatation of the cervix and uterine contractions).

Prostatectomy: surgical removal of the prostate.

Puerperal: relating to childbirth. **Rad**: unit of absorbed radiation.

Radiotherapy: treatment using ionizing radiation. **Re-anastomosis**: surgical joining of two organic ducts.

Retrograde ejaculation: abnormal ejaculation, with the ejaculate ending in the bladder.

Rhesus (Rh) factor: agglutinogen found on the blood cells of 85 percent of people (Rh positive), and not on the blood cells of the other 15 percent (Rh negative).

Salpingitis: inflammation of a fallopian tube.

Semen analysis: laboratory examination of the semen and sperm.

Spontaneous abortion: miscarriage.

Sterilization: operation that renders a living being incapable of reproducing.

Stroma: supporting and binding tissue of an organ.

Submucosal: under the mucous membrane.

Suction curettage: technique characterized by dilatation of the cervix and curettage of the uterus with a hollow curette through which suction is applied.

Sympathetic innervation: autonomic nervous system. **Synechia**: pathological cicatricial joining of two surfaces.

Tonsillectomy: surgical removal of the tonsils.

Toxaemia of pregnancy: hypertension during pregnancy.

Transcervical: that goes through the cervix.

Tubal: relating to the fallopian tubes.

Tubal dropsy: cystic form of an infection of the fallopian tubes. **Tubal insufflation**: injection of gas into the fallopian tubes.

Tumour: abnormal growth of tissue. **Umbilical**: relating to the umbilicus. **Urethral**: relating to the urethra.

Vacuum extractor: suction device used to facilitate expulsion of the head of the

fetus during delivery.

Vas deferens: the duct that conveys spermatozoa (plural: vasa deferentia).

Vasectomy: masculine sterilization.

Vasography: radiographic examination of the vasa deferentia.

Vasovasostomy: surgical intervention to reconnect the vasa deferentia.

Villi: hair- or finger-like vascular processes on certain surfaces of the body.

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Occupational and Environmental Exposure Data: Information Sources and Linkage Potential to Adverse Reproductive Outcomes Data in Canada

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Executive Summary

This study investigates the feasibility of record linkage as an approach to determining the possible effects of environmental or workplace agents on reproductive health.

The authors review the history of record linkage in Canada and discuss its advantages for combining data from different sources to provide a potentially powerful set of data for analyzing long-term health risks associated with specific agents. Examples are provided of the application of record linkage in Canada to study occupational exposures and adverse human health effects.

In collaboration with a similar study by the Flett Consulting Group, this study identifies and assesses exposure and outcomes data bases that might be useful for improving the understanding of risk factors that may adversely affect reproductive health. The data bases are classified according to their probable record-linkage potential and cross-tabulated with specific outcomes and exposures.

The authors note the need for further investigation to corroborate the feasibility of record linkage using the identified data bases and for more information about occupational and environmental exposure generally.

Exposure and Outcomes Data Bases and the Value of Record Linkage

Introduction

Health hazards in the environment and in the workplace are increasingly causing concern to many people throughout the world. These issues have caught the attention of scientists, politicians, women's groups, workers, environmentalists, and other groups of concerned individuals. More recently, the negative effects on reproductive health have attracted a specific focus of attention. Despite growing concern, however, there are few definitive studies on this subject (U.S. Congress 1985, 422).

Several factors have contributed to the general lack of information on reproductive health effects. Traditionally, toxicological evaluations of chemicals seldom considered the effects on reproductive health. In some instances, pregnancy, miscarriage, and congenital birth defects were studied, but rarely did toxicological studies examine the effects of harmful agents on gametes, hormones, or, more generally, couple infertility (Baird and Wilcox 1986). This is also partly a reflection on our level of understanding of human reproduction.

There are many other reasons why information is lacking. For example, suitable methods to measure various reproductive outcomes and their associated health hazards have not been adequately developed. This has made it difficult to identify cause-effect relationships between suspected risk factors and adverse reproductive health outcomes. In some cases, this problem is compounded by a lag period of years or decades between the time of first exposure and the time the problem eventually arises. Further complications arise in the difficult, if not impossible, task of trying to sort out the effects of other influences on reproductive health, such as lifestyle or heredity. In the face of these difficulties, there has been increased public demand for specific information on the long-term risk associated with various living and working environments (Bueckert 1991; Marlin 1991; Lipovenko and McLaren 1985).

A wide range of different research approaches has been required to investigate the possible effects of environmental or workplace agents on reproductive health. Each type of research has its own particular benefits and drawbacks. For example, toxicological studies often use animals as their subjects. Animals are given specific doses of an agent under controlled conditions. The results of these studies can then be used to predict whether or not an agent threatens the reproductive health of the animal being tested. This information, however useful, cannot be directly applied to human beings because there are no reliable means to convert

dose-response relationships from animals to humans. Additionally, for most agents, little information is available on the levels to which people have been exposed.

Another valuable research approach is epidemiological studies. These studies use a variety of statistical tests on large populations to determine if there are associations between health problems and particular risk factors or exposures. These tests compare information on a form of "exposure" (such as type of job, environmental factors, or amount of exposure to a chemical or radiation) and a type of "outcome" (a particular form of long-term health problem or a specific end point).

The associations that result from epidemiological studies are often sought for practical purposes, such as setting exposure limits, preparing cost-benefit studies, or priority setting. In a strict, scientific sense, epidemiological research is not able to prove that a particular exposure definitely causes a specific observed effect. Rather, it can show that there is (or conversely, is not) an association between exposure and outcome variables. This association must then be taken a step further by generating a hypothesis and testing it.

Epidemiological research, however, has inherent limitations. For example, by the time an association is established between an environmental exposure and an adverse outcome, extensive damage may have already occurred in the reproductive system of many. Epidemiological studies that have data missing or small population sizes may not be able to arrive at conclusive results. Even if statistically significant results are obtained, the results can be interpreted in a variety of ways, making it difficult to assess the impact of occupational and environmental factors on human health. This is particularly true for the detection of long-term health problems such as cancer (Yassi 1987). In such instances, uncertainties and controversies have been used to justify delays in setting standards, establishing regulations, and granting compensation.

The Use of Records for Evaluation of Reproductive Risks

Health professionals from all sectors of the workplace have been examining the possibility of using statistical information to help in determining the nature and magnitude of harmful agents. Such an approach envisions the extensive collection of data on human exposures and linking this to information in other data sets on short-term and long-term health outcomes in these individuals. This approach may make it possible to conduct analyses of large data sets that would allow conclusions to be reached and identify risk factors. For a variety of reasons, although the concept of this approach is straightforward, the reality of implementing it is not easy, and there are practical difficulties.

First of all, the many potentially useful sources of data are scattered across Canada and held by many different jurisdictions. Some of the better known examples include the workers' compensation system, health care

insurance system, and cancer and mortality registries. Each has its own particular value and limitations.

Workers' compensation data are considered the most comprehensive single source of information, but the system is flawed for disease surveillance purposes. The structure and application of its coding systems vary across Canada, and the data bases in each jurisdiction reflect the non-uniform character of different compensation systems. There are differences in the rate of reporting and in the formal administrative criteria governing the acceptance of claims. The recording of occupational illnesses (as opposed to injuries) is particularly limited and inconsistent. It is also difficult to modify these data sources to serve the needs of disease surveillance because they have been established for distinctly different purposes. These include the adjudication of claims, which must be submitted within 72 hours so that the process can proceed promptly (Spiegel and Yassi 1991).

Data from the health insurance system — hospital separation forms, physician reporting forms, emergency room reports, birth registries, etc. — are able to provide detailed information on the occurrence of health events. These systems, however, seldom contain information regarding workplace or environmental exposures of these same individuals. Some sources, such as death certificates, list information on "occupation," but the quality of this information is considered grossly inadequate (Spiegel and Yassi 1991). It is therefore necessary to link the records on these "end points" to data sets containing information about exposures of these same individuals. With regard to cancer and disease registries, Canada has two of the world's best centralized follow-up facilities — the Canadian Mortality Data Base and the National Cancer Incidence Reporting System, administered by Statistics Canada.

Along with these limitations, there are other basic challenges that must be addressed before statistical information can be used effectively to identify risk factors and serve those potentially affected by the risks. Conclusions from statistical analyses are only as good as the quality of information that was analyzed. It is critical that specific definitions (for specific occupational diseases or exposures, for example) be developed and consistently applied to the information being collected. Standard protocols for collecting, coding, and reporting the information are also important.

These concerns have been discussed in a recent series of tripartite workshops across Canada (Canadian Centre for Occupational Health and Safety 1989).

Also, in collecting medical data, it is essential that people are protected against their unauthorized release (for example, the misuse of confidential medical information could compromise a person's work status or reduce his or her possibility for promotion). Breach of confidential medical or personnel information places an employer at risk of civil litigation, with legal consequences described in legislation protecting the confidentiality of medical records. These risks must be balanced by the benefits produced

through the collection and maintenance of comprehensive collections of health records.

The fact remains that statistical answers to questions concerning risk factors commonly require information with qualities not found in existing separate statistical information resources. Ideally, the information should include all significant events and health status throughout the major portion of an individual's life (and the lives of family and children). This does not exist in any single data base. The only way to get such information is to bring together statistical records for the same individual from a variety of different sources — birth records, hospital records, and personnel records. Even though the statistics may have been collected by various organizations for various reasons, when combined they may provide a potentially powerful set of data suitable for analyzing the long-term health risks associated with specific agents.

A process is available for this purpose. It is called record linkage.

The Value of Record Linkage

The term *record linkage* was first used in 1946 by Dr. Halbert Dunn, Chief of the United States National Office of Vital Statistics. It describes a process of assembling statistical information on individuals by uniting statistical records collected and stored in different sources throughout the lifetime of the person and the person's family (Smith 1982; Fair 1989, 1992).

Over the years, record linkage has developed into a very powerful and valuable analytical tool. It has enabled researchers to take massive amounts of information from two or more sources and combine them to conduct reliable statistical studies that otherwise would not have been possible. Record linkage also allows new information to be extracted from existing sources that on their own may not have been particularly useful.

Record linkage is particularly useful for analyzing large amounts of information on large populations. This technique is especially important for studies that investigate the long-term effects of low-level exposure to agents that do not have a minimum level of exposure without hazard.

In general, record linkage enhances conventional epidemiology because it allows researchers to take advantage of pre-existing resources to assess relatively large populations at comparatively low cost. As record-linkage studies have the potential for producing more definitive results, they could reduce some of the uncertainty found in conventional epidemiology. As a result, record-linkage techniques can have an important role to play in assessing potential hazards affecting long-term health problems, especially those associated with reproductive health.

History of Record Linkage in Canada

Canada has a strong heritage of record-linkage research. Dr. Howard B. Newcombe, a pioneer in the development of computerized record-linkage techniques, first described methods for record linkage in 1959.

The primary concern of early linkage studies was to investigate the risks of congenital disease in the general population of Canada. These studies focussed on linking information about family members (such as parents and children or cousins) with various health records relating to death, handicaps, congenital anomalies, and hospitalization to create personal histories grouped within parent-offspring relationships (Fair 1989).

In the last two decades, the major focus of record-linkage studies has been on individual follow-up studies. These types of studies link statistical records containing information on an individual's possible exposure to an environmental or occupational factor with individual medical records containing information on long-term disease or particular end points. At present, the focus is largely on the associations between specific agents and the subsequent development of cancer (Fair 1989), although this is broadening.

Canada is particularly well equipped for research involving recordlinkage studies. Both federal and provincial agencies have worked for many years to develop health and mortality files.

The development of these capabilities has made it possible to reduce the cost and increase the scope and scale of long-term medical follow-up investigations. Canada has developed a unique, machine-readable mortality data base. It contains over six million deaths dating back to 1950 and a system for linking these records to other personal or medical files. This system, called the Generalized Iterative Record Linkage System (GIRLS), is run by Statistics Canada. It is a *probabilistic* linkage program that combines records pertaining to an individual from two (or more) files. These capabilities should offer considerable advantages to researchers interested in studying possible reproductive outcomes (Fair 1989). These benefits, however, depend on the continued collection of data in a standardized form that allows record-linkage studies. Without such standardization, the possibility of record linkage is lost.

Examples of Record-Linkage Studies in Canada

Researchers have completed several studies that employed record linkage to successfully link occupation-related disorders to occupational exposures. However, there appear to have been very few attempts to link occupational exposures and reproductive outcomes. This is an area with the potential to yield very important results in future record-linkage projects.

The following examples of record-linkage applications have been reviewed to illustrate how the technique has been applied to shed light on occupational exposures and adverse human health effects. Although some

Example: Olshan et al. 1990

The authors conducted an exploratory case-control study of paternal employment as a firefighter and the risk of birth defects among offspring. Cases of birth defects were identified from the British Columbia Health Surveillance Registry. This registry uses 60 different registering sources, including birth notices, hospital administration/separation forms, and death/stillbirth records. From registry records, 22 192 live-born children with birth defects were identified for the period 1952-1973.

For each birth, paternal occupation was obtained by linkage with the birth registration record, where this information was routinely recorded for the years 1952-1973. From the B.C. birth file for the years 1952-1973, two normal controls were matched to each case on month, year, and hospital of birth. For each category of birth defect, two comparisons were made. The first examined the ratio of firemen to all other occupations of fathers of children with defects versus the corresponding ratio in controls. The second comparison restricted the occupation to policemen because they are likely to be similar to firemen with respect to socioeconomic status and hiring criteria. The data of this study suggest that paternal employment as a firefighter increased a child's risk of being born with ventricular or atrial septal defects. This study had the advantage of being based on a large number of cases systematically ascertained from a population-based registry system, with a large control group being available from birth files.

Example 2: Roberts et al. 1989

The objective of this study was to investigate mortality rates in nickel workers due to various causes (particularly respiratory cancer) and to relate any observed risks to the environmental contaminants. This is a historical-perspective mortality study of 54 509 Inco workers. All male Inco employees who had worked for the company for six months or more were followed for mortality during a 35-year period (January 1950 to December 1984) by computerized record linkage to the Canadian Mortality Data Base (CMDB).

From company records, 15 058 workers were known to be alive at the end of 1984. In addition, from company benefits records, 5 932 workers were known to have died prior to 1985. The remaining 33 519 workers who had left Inco during the follow-up period formed the group of unknown mortality status. The mortality of the cohort was determined by record linkage with the CMDB at Statistics Canada. The record-linkage service provided by Statistics Canada attempted a match between the 54 509 workers and death certificates based on agreement in surname, given names, and birth date. Record linkage identified an additional 2 455

subjects who had died. The remaining 31 064 workers who had left the company and who were not found to have died in Canada have been assumed to be alive. This assumption, which places great faith in the record-linkage procedure, can be justified by two facts.

First, record linkage recognized death in 92 percent of the 5 932 workers known, from company records, to have died. The death certificates of the elusive 8 percent were tracked down manually. They were not recognized by record linkage because of missing or incorrect information.

Second, an independent follow-up of a sample of 1 000 workers of unknown status was carried out. Sixty-three of the 925 workers who were traced were found to have died. Of these 63, record linkage failed to detect 5 (7.9 percent). The data point to a mortality ascertainment from record linkage of 92 percent. However, if we consider the possible influence of the 75 subjects not included in the independent follow-up, it would appear that record linkage would recognize 95 percent of the total deaths. A 95 percent ascertainment rate is methodologically acceptable by epidemiologic standards.

In this study, record linkage provided a complete mortality ascertainment process on an exceptionally large cohort. The results of this study are being used for setting respiratory standards.

Example 3: Dodds 1991

This study had three objectives:

- 1. to determine whether the offspring of cancer patients are at an increased risk of having a child with a congenital anomaly;
- 2. to determine whether treatment for cancer increases the risk of having a child with a congenital anomaly and, if so, which treatments are responsible for the increase; and
- 3. to assess, to the extent possible, whether cancer therapy could be responsible for germ cell mutations, causing an increased risk within certain subgroups of congenital anomalies.

This is a case-control study where cases were defined as the parents of children with a congenital anomaly registered as Ontario residents in the Canadian Congenital Anomalies Surveillance System (CCASS) between 1979 and 1986.

Parents of the children with birth defects were identified by a computerized record linkage between the CCASS and the Ontario birth certificate files. The identifying variables used for the record linkage were child's surname, given name, sex, birth data, birthplace, and birthweight; and mother's initials, age, residence, and duration of pregnancy. The total number of CCASS cases with links to birth certificates was 49 557 (96.8 percent of the total number of CCASS records). An equal number of matched controls were selected from the Ontario birth certificate files. The study file of case and control parents was then linked to the Ontario Cancer Registry to identify parents with a previous diagnosis of cancer. The

identifying variables used in the linkage were surnames, given names, birth year, sex, birthplace, and residence code. The results of this study suggest that, overall, those who have had cancer or who have been treated for cancer are not at an increased risk of having a child with a congenital anomaly.

This is an extensive record-linkage study that apparently has produced useful new information on birth defects and cancer treatment exposure linkage.

Example 4: Ritter et al. 1990

This study was initiated to assess the risks of cancer in relation to pesticides and other agricultural exposures among Canadian farm operators. It presented results of the analysis of 70 000 male Saskatchewan farm operators, a subset of 365 000 Canadian farm operators identified in 1971 by the Census of Agriculture. This study involved the use of four data bases: (1) 1971 Census of Population, (2) 1971 Census of Agriculture, (3) Canadian Mortality Data Base, and (4) 1981 Central Farm Register of the Canadian Farmer.

To study the mortality experience of the Saskatchewan farmers, the authors used a computerized record linkage of data obtained from the Central Farm Register, the Census of Agriculture, the Census of Population, and the Canadian Mortality Data Base. The authors observed that proportionate mortality ratios demonstrated a pattern of mortality within the study group: low lung cancer mortality and higher-than-normal mortality from stomach and prostate cancer, non-Hodgkin's lymphoma, and aplastic anaemia. Overall death rates (25 percent) were considerably lower than for the general male population. This study found a relationship between non-Hodgkin's lymphoma mortality and acres sprayed with herbicides. It also found that a link exists between expenditure of fuel oil and risk of death from non-Hodgkin's lymphoma.

Example 5: Silins et al. 1985

The purpose of this study was to relate overall and cause-specific perinatal mortality rates to vital statistical data available on birth certificates. The objective was to investigate, with Canadian data, any associations that may exist between variables reported on birth certificates, stillbirth records, and infant death certificates.

This was a population-based, computerized record-linkage study of infant births and deaths in 1978 and 1979 in eight Canadian provinces. It was undertaken to permit analysis of perinatal mortality in relation to maternal and infant characteristics. Quebec and Newfoundland data were excluded because of lack of certain information on the birth records supplied: Quebec does not supply names in machine-readable form for either births or deaths, and the birth certificates from Newfoundland did not include the variables of interest.

The data studied consisted of information on 3 118 stillbirths (28 weeks' or greater gestation) and 510 425 live births that occurred

during 1978 and 1979, and on 3 076 corresponding deaths in the first week of life during 1978, 1979, and 1980. The files used were the vital statistics data bases at Statistics Canada. Deaths of infants before one year of age were linked to live births by means of GIRLS.

The authors conclude that perinatal mortality rates were significantly higher in non-urban than in urban areas. Also, about 75 percent of early neo-natal mortality was attributable to low birthweight or fetal immaturity (less than 2 500 g). The authors also conclude that greater emphasis should be placed on the prevention of low birthweight.

This study had a high degree of completeness of the population since all but 3 percent of deaths in the first week of life were linked to the appropriate births. We also feel this study was done thoroughly and with due regard for proper methodology. The methods used to analyze the data in this study included logistic regression, which was used to assess the effects on perinatal mortality of several variables, such as maternal age and record of previous stillbirths. The authors of this report are in senior government positions in the epidemiology and congenital anomalies data field in Canada.

Example 6: Abbatt and Newcombe 1981

This study evaluated the radon risk to Eldorado workers who mine and refine uranium. It had two objectives:

- 1. to obtain dose-response data with which to evaluate the risks to workers in radon- and radon-daughters-containing atmospheres, and to provide additional quantitative information on which to base possible improvements in working conditions;
- 2. to identify any employees of Eldorado Nuclear Limited (ENL) whose cause of death suggests that a potential right to make a compensation claim exists for their survivors, and to similarly identify living ex-employees of ENL whose work histories and status of health suggest a potential right to make a compensation claim.

This was a retrospective cohort study merging into a prospective cohort study. The study population consisted of all Eldorado employees who had ever worked for ENL and for whom records were available. The total nominal roll was approximately 21 000 and consisted of employees of the mining, refining, research and development, aviation, and exploration divisions. Eldorado developed the Nominal Roll, Work History, and a Dose History as separate files. When the Nominal Roll was ready, Statistics Canada used it to search the CMDB for records of deaths of the relevant individuals and transmitted the results minus names to the National Cancer Institute of Canada. The Work History and Dose History files were also sent to the Institute, which had a memorandum of understanding with ENL to analyze, interpret, and publish data related to the study. The preliminary results showed that lung cancer was present in excess for the

mining sites, and a few other causes of death appeared to be in excess (violence, alcoholism, and cirrhosis of the liver).

The preliminary results also showed that computerized record linkage is considerably more accurate than a conventional manual linkage.

This study allowed the compensation system to adjudicate and compensate claims related to lung cancer.

Summary

As the studies indicate, application of data linkage has played an important role in research in Canada, but there is a need to develop this application further. There are few studies that attempt to link occupational and environmental exposure data bases with data bases dealing with adverse reproductive outcomes, yet this is an important area on which to have information in order to guide policy.

The application of data-linkage methodology, however, is contingent on a number of factors, not the least of which is the need for accurate, comprehensive, consistent record keeping. With appropriately stringent privacy protections regarding access to named data, linking records on the Canadian population would undoubtedly benefit our society in the long run.

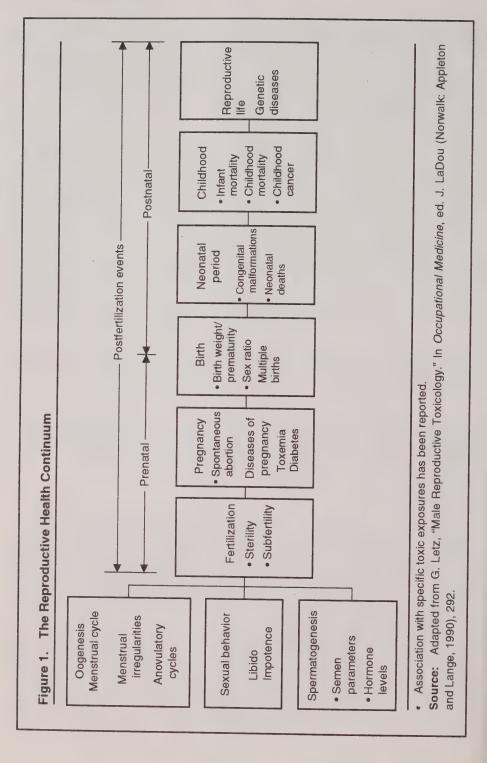
The following sections of this paper examine issues around occupational and environmental exposure and adverse reproductive outcomes. Potential data bases are identified and assessed for their linkage potential.

Exposure and Outcomes Data Bases: Some Canadian Sources of Potential Interest to Improving Understanding of Infertility

Introduction

The objective of this section of the project is to conduct a search for sources of statistical information — exposure and outcomes data bases — that could be useful in improving the understanding of risk factors adversely affecting reproductive health. The final section of this report will examine if record-linkage potential exists between the located sources of information. The first step — locating such sources of information — is a challenge for several reasons.

One reason has been the traditional view that reproductive health concerned only the effects of chemicals on pregnant women. Only recently has the scope of reproductive health been fully appreciated. As shown in Figure 1, it is a broad continuum of processes and events that involve both genders, and encompasses the cycle spanning the initial production of gametes through to the growth, development, and reproduction of the offspring.



With this broader concept, the list of reproductive health hazards increases to include substances, agents, or processes capable of adversely affecting the reproductive function in men or women, the developing embryo, the fetus, or the health and reproductive ability of the offspring. The range of adverse reproductive outcomes runs along a continuum that moves from disorders causing delay or lack of conception (e.g., menstrual disorders, hormonal problems, impotence, sperm abnormalities, uterine fibroid, tubal occlusions), to adverse affects on pregnancy (e.g., toxaemia, spontaneous abortions), to adverse birth outcome (e.g., stillbirth, low birthweight, congenital anomalies). As shown in Figure 1, the continuum extends even further, in that exposures of the parents may have adverse effects on child health and development.

Although it is now recognized that the effects of toxins may occur on any aspect of this continuum, not all of the possible adverse outcomes have been studied in detail. For example, there is little information available on impotence, delay in conception, and early embryonic or fetal death. Because of this, it is not possible for the project to focus on a totally inclusive list of adverse reproductive outcomes. The list of outcomes was chosen based on the extent of existing knowledge about them and their status as priority issues. These outcomes include menstrual disorders, spermatogenesis disorders, hormonal disorders (male and female), abnormalities of the cervix, spontaneous abortion, toxaemia (preeclampsia), stillbirth, low birthweight, congenital anomalies, childhood cancer, and childhood development.

Some examples of reproductive hazards are listed in Table 1, classified into each of four categories — chemical, physical, microbiological, and psychosocial. Animal tests have implicated other agents, but there is a lack of suitable studies involving human populations, so that the effects on humans are unknown. A recent report prepared for the Federal-Provincial Advisory Committee on Environmental and Occupational Health provides a thorough discussion of adverse reproductive risk factors and the evidence supporting their identification (Canada, Health and Welfare Canada 1987).

Exposure data bases rarely include information that is directly related to reproductive events, but they can include other information that allows linkages and associations to be made between exposure and information on outcome. If it were possible to make linkages for numbers of individuals, then lists of specific exposures and their duration, detailed work and medical histories, et cetera, could all contribute to increasing our knowledge of the effects of the environment and occupations on reproductive health. Due to the vast numbers of occupational and environmental exposures possible, this study is restricted to physical and chemical hazards, including radiation, noise, temperature, lead, carbon monoxide, dioxin, solvents, and the pesticide dibromochloropropane (DBCP).

Table 1. Clas	ssification of	of	Putative	Reprodu	ctive	Hazards
---------------	----------------	----	-----------------	---------	-------	---------

Female Hazard ca	ategory Male
СНЕМІ	CAL
Meta	ils
Lead	Lead
Mercury	Mercury
Pestic	ides
Aldrin, dieldrin	1,2-dibromo-3-
Chlordecone	chioropropane
	Chlordecone
Sterilizing	Agents
Ethylene oxide	
Therapeuti	c Agents
Oestrogens	Oestrogens
Chemotherapeutic	Chemotherapeutic
agents	agents
Organic S	Solvents
Styrene	Carbon disulphide
Other Ch	emicals
Anaesthetic gases	
Polychlorinated biphenyls	
Polybrominated biphenyls	
Polybrominated biphenyls PHYSI	CAL
PHYSI Radiation -ionizing	Radiation -ionizing
PHYSI Radiation -ionizing -non ionizing	Radiation -ionizing -non ionizing
PHYSI Radiation -ionizing -non ionizing Noise	Radiation -ionizing -non ionizing Environmental
PHYSI Radiation -ionizing -non ionizing Noise Vibration	Radiation -ionizing -non ionizing
PHYSI Radiation -ionizing -non ionizing Noise Vibration Physical exercise	Radiation -ionizing -non ionizing Environmental hyperthermia
PHYSI Radiation -ionizing -non ionizing Noise Vibration Physical exercise MICROBIO	Radiation -ionizing -non ionizing Environmental hyperthermia
PHYSI Radiation -ionizing -non ionizing Noise Vibration Physical exercise MICROBIO Virus	Radiation -ionizing -non ionizing Environmental hyperthermia
PHYSI Radiation -ionizing -non ionizing Noise Vibration Physical exercise MICROBIO	Radiation -ionizing -non ionizing Environmental hyperthermia LOGICAL Virus
Radiation -ionizing -non ionizing Noise Vibration Physical exercise MICROBIO Virus Bacteria	Radiation -ionizing -non ionizing Environmental hyperthermia LOGICAL Virus
PHYSI Radiation -ionizing -non ionizing Noise Vibration Physical exercise MICROBIO Virus Bacteria PSYCHO	Radiation -ionizing -non ionizing Environmental hyperthermia LOGICAL Virus SOCIAL
PHYSI Radiation -ionizing -non ionizing Noise Vibration Physical exercise MICROBIO Virus Bacteria PSYCHOS	Radiation -ionizing -non ionizing Environmental hyperthermia LOGICAL Virus SOCIAL Tobacco

Source: Adapted from E.C. McCloy, "Reproduction and Work," in *Hunter's Diseases of Occupations*, ed. P.A.B. Raffle et al. (Boston: Little, Brown, 1987), 957.

Methodology to Identify Data Bases

1. Definition of Data Base

In general terms, a data base is a collection of data organized especially for rapid search and retrieval. Data bases have also been defined as collections of numeric data and/or textual information that are processed into computer-readable form or printed materials, often for electronic distribution (*Directory of Online Databases* 1990).

A data base can range from a small number of records manually maintained, to a massive computer data base, such as the CMDB. For the purpose of this report, a data base should include a sufficient number of records to be used for statistical purposes. Important considerations in choosing data bases for inclusion are the usefulness of the records relevant to our concerns and the ability of the data to be linked.

2. Investigative Methods

In this section, we identify and tabulate data bases that, on initial examination, could potentially provide information on occupational exposure or health problems relating to adverse reproductive outcomes. The collection of data bases is not intended to be totally inclusive: our interest is restricted to a representative list of the selected exposure agents and reproductive outcomes described above.

The geographic coverage for the data bases is restricted to Canada, with the exception of Great Lakes data, which may also include information from the United States. The time period searched covered at least the last 10 years.

A broad, extensive approach was used to locate the most current and comprehensive information about national, provincial, and private data bases in Canada. This approach included a variety of activities.

To investigate federal and provincial government data bases, personal contacts were made with federal and provincial government agencies and officers responsible for the relevant data bases at Statistics Canada, Environment Canada, Health and Welfare Canada, the Ontario Cancer Treatment and Research Foundation (OCTRF), et cetera.

To locate additional information on data bases that could contain data on environmental exposure, we contacted the Secretary to the International Joint Commission's Virtual Elimination Task Force. As well, occupational hygiene departments of large industries were contacted.

Computer searches were conducted on two data bases created and maintained by the Canadian Centre for Occupational Health and Safety — CANADIAN STUDIES and CANADIANA. We also located three reports on environmental data bases in Canada. These were "Environmental Data Bases for State of the Environment Reporting" (Keddy 1989); "Environmental Databases for State of the Environment Reporting" (McRae 1990); and "Databases for Environmental Reporting: Federal Government

Departments, Excluding Environment Canada" (Canada, Statistics Canada 1991).

Literature searches were also conducted on bibliographic data bases — NIOSH and MEDLINE — to locate published studies that suggested the existence of little-known or hard-to-locate data bases. Two basic approaches were employed. One was to search for studies on general or specific reproductive outcomes in relation to automated data processing systems, medical records, and birth certificates. The other approach was to search for studies on the specific occupational and environmental agents in relation to reproductive outcomes.

Data Bases Identified

Tables 2 and 3 list the data bases that we have identified as potentially relevant for linking occupational and environmental exposures to adverse reproductive outcomes. The inventory identifies the data base (or studies that may have data bases) and, where possible, the source of the data base or contact person, the system, and the founding organization.

Preliminary Identification and Assessment of Record-Linkage Potential of Exposure and Outcomes Data Bases Relevant to Adverse Reproductive Outcomes

Introduction

The general purpose of this project has been to examine the feasibility of linking various occupational and environmental exposure data bases with adverse reproductive health data bases. The first section reviewed the Canadian record-linkage experience with respect to environmental and occupational exposure and reproductive health outcomes as represented in the published literature. We also contacted researchers in the field of reproductive health to gauge informally the importance of reproductive health issues and the perceived need for investigating the feasibility of record-linkage studies.

The second stage of this project identified and tabulated data bases that may be able to provide exposure and outcome information relating to this project. For this, we selected specific outcomes and specific exposures to search for published and unpublished literature using external and in-house data bases. This approach was complemented by informal contact with experts representing industry, academia, government, and labour across the country. They provided valuable information not available in conventional sources that assisted in completing the search for data bases.

This section further examines the record-linkage feasibility of data bases identified in the previous section of this project. To facilitate this,

a questionnaire was developed and distributed as a preliminary step in collecting specific information on key features of data bases with respect to exposure data, outcome data, and record-linkage potential. Information from the questionnaires was tabulated and analyzed and the results were discussed within the context of a preliminary report on record-linkage potentials for studies dealing with reproductive health.

Methodology

Collaboration for Development and Distribution of the Questionnaire

In the course of data base investigation, a collaboration was developed between this project and a related project from Group 2 of the Research and Evaluation Division of the Royal Commission on New Reproductive Technologies undertaken by the Flett Consulting Group. Their project involved the assessment of record-linkage feasibility to extend knowledge on the relation between risk factors (such as poverty, nutrition, fitness, sexually transmitted diseases, etc.), birth outcomes, and child health outcomes.

Prior to our collaboration, the Flett Consulting Group had already developed a questionnaire to assess data base record-linkage feasibility according to three general descriptor areas:

- general data base characteristics
- technical characteristics
- ownership and access*

The Flett questionnaire had been reviewed and successfully tested by experts in the field of record linkage. Since all of the outcome data bases identified in our project were included within the list of outcome data bases in the Flett Consulting Group's project, an agreement was made that they would administer the distribution and analysis of questionnaires dealing with outcome data bases.

For the exposure data bases in this project, an additional descriptor dealing with occupation or environmental data was added to the questionnaire. Following initial telephone contact with guardians of the data bases or their associates, the questionnaires were distributed, but only to those who had consented to consider responding to it (see Appendix 1).

Questionnaire Analysis

Information on exposure data bases retrieved in the questionnaires was catalogued and evaluated. The Flett Consulting Group provided us with copies of completed questionnaires from the guardians of outcome data bases. Record-linkage feasibility was classified according to criteria

^{*} For details of these general descriptors, see Hayward et al. 1993.

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			Occupational and Enviro	птепа Ехро	sure Data 53
	data on contaminant levels in fish from the Canadian Great Lakes	uses vital statistics, hospital records, CCASS, and chemical data bases		1977 to present	
	Statistics Canada	CANADIAN STUDIES, uses vital statistics, CANADIANA data hospital records, bases data bases	(Fran Wortman)		
stillbirth, congenital anomalies, childhood cancer	trace organics (whole body concentration in fish)	birth defects, stillbirths	ecological study to determine the effect of agricultural chemicals on reproduction; data include exposure and outcome information, including maternal occupation (not certain how far back the data have been collected)	noise, copper, nickel ion, trace elements	various
(IRSST) (now at London Chest Hospital, UK, 44-81-980-4433)	D.M. Whittle, Fisheries and Oceans Canada (416) 336-4565	Dr. F. White, Dalhousie University, Task Force on Chemicals in the Environment and Human Reproductive Problems, New Brunswick	Fran Wortman, PEI Reproductive Health Program, Dept. of Health (907) 566-3934	John Ashton, Inco Limited, Manitoba Division (204) 778-2500	Carl Whicher, Alcan, Kitimat (604) 639-8375
	Great Lakes Contaminants Surveillance Program	Chemicals, Birth Defects and Stillbirths in NB	Prince Edward Island (PEI) Reproductive Care Program	Occupational Exposure Monitoring Program	Industrial Hygiene Management System

Name of data base	Contact person and organization	Selected exposures or outcomes	Source of information	Features
National Dose Registry (NDR) (also known as Lifetime Dose History File)	Pat Ashmore, Occupational Radiation Hazards Division, Bureau of Radiation and Medical Devices, Health and Welfare Canada (613) 954-6660	occupational radiation	telephone call (W. King)	includes uranium mines radon exposures and personal dosimetry records from Ontario, Quebec, New Brunswick Power, and Atomic Energy Canada Limited (AECL)
Aircraft Noise Exposure Forecast	Mr. Leo Marti-Aguilar, Canada Mortgage and Housing Corporation (613) 748-2264		Statistics Canada	contour maps at 1:50 000 scale of current and forecast noise levels in the vicinity of airports in Canada
Hospital Morbidity Database	Mr. Cyril Nair, Chief (613) 951-8387; Mr. Rod Riley, Statistician; Health Care Section, Canadian Centre for Health Information (CCHI), Statistics Canada	spontaneous abortion, congenital anomalies, menstrual, hormonal, and reproductive system abnormalities, cancer, surgical procedures; International Classification of Diseases (ICD)	Gentleman (1991)	data are recorded on an event (separation) basis, not on a person (patient) basis; therefore, not linkable by personal identifiers
Association Between Birth Defects and Exposure to Ambient Vinyl Chloride	G. Theriault, Laval University (for U.S. Environmental Protection Agency)			

Table 3. Outcomes Data Bases	Contact person and Selected exposures Name of data base organization or outcomes	Birth File Dr. Jane Gentleman, Chief low birthweight, number Gentleman (1991) (613) 951-8553; of stillbirths (32 data Mr. S. Wadhera, elements) Statistician; Health Status Section, CCHI, Statistics Canada	Stillbirth File Dr. Jane Gentleman, Chief kind, weight, and (613) 951-8553; number of stillbirths Mr. S. Wadhera, (42 data elements) Statistician; Health Status Section, CCHI, Statistics Canada	Death File Dr. Jane Gentleman, Chief immediate and antecedent causes of Mr. S. Wadhera, death (ICD-9) including Statistician; Health Status perinatal death Section, CCHI, (stillbirth), cancers
		iht, number Ger 32 data	hs (s	ses of ncluding ers
	Source of information	ıtleman (1991)	Gentleman (1991)	Gentleman (1991)
	Features			causes of death are coded according to ICD-9

posures Source of Features	Gentleman (1991)	calls (Dr. G. Sherman information are stillbirths and K. Johnson) ated Vital ata Base) CCASS is subset derived directly from Hospital Medical Records Institute, no risk factors, no cancers, occupation possible	childhood Gentleman (1991) all deaths in Canada childhood since 1950 lbirths, thomalies
d Selected exposures		Kenneth C. Johnson, Head, congenital anomalies Birth Defects and (birth defects — 1st Poisonings Section, Bureau year of life), stillbirths of Chronic Disease (from Integrated Vital Epidemiology, Hospital Statistics Data Base) Medical Records Institute (HMRI) (613) 957-0339; and the Bureau of Chronic Disease Epidemiology, Disease Sof Infants and Children, Laboratory Centre for Disease Control, Health and Welfare Canada	ior deaths from low birthweight, childhood cancers, stillbirths, congenital anomalies
Contact person and	Dr. Jane Gentleman, Chief (613) 951-8553; Mr. S. Wadhera, Statistician, Health Status Section, CCHI, Statistics Canada	Kenneth C. Johnson, Head, Birth Defects and Poisonings Section, Bureau of Chronic Disease Epidemiology, Hospital Medical Records Institute (HMRI) (613) 957-0339; and the Bureau of Chronic Disease Epidemiology, Disease of Infants and Children, Laboratory Centre for Disease Control, Health and Welfare Canada	Anna Brancker, Senior Analyst, Health Status Section, CCHI, Statistics Canada
Table 3. (cont'd)	Canadian Health Indicators Database	Congenital Anomalies (Birth Defects)	Canadian Mortality Data Base

year, complete parental information, case-control use, Ontario Hydro interested in using this data base in future		coded by primary site, so not useful when coding certain childhood cancers
(L. Marrett)	telephone call (Asha Nambyarooran)	
congenital anomalles, radiation	includes data on 0 to 19-year-olds with musculoskeletal disorders or other malformation as reported by Easter Seal Nurses; statistics maintained by age and disability, according to ICD-9; no information on parents (not mandatory); sometimes information on birth trauma or prenatal use of drugs, medication, alcohol included	childhood cancers
Hanna Welr, OCTRF (416) 423-4240; Lorraine Marrett, OCTRF (416) 978-6635	Asha Nambyarooran, Easter Seal Society (416) 421-8377	Dr. Jane Gentleman, Chief (613) 951-8553; Ms. Leslie Gaudette, Statistician; Health Status Section, CCHI, Statistics Canada
Anomalies Database (Ontario)	Easter Seal Client Registry	Cancer Incidence File

Name of data base	Contact person and organization	Selected exposures or outcomes	Source of information	Features
Oxford Database of Perinatal Studies	Dr. Murray Enkin, Chedoke- low birthweight, McMaster Hospital childhood cance stillbirths	low birthweight, childhood cancers, stillbirths	Chalmers et al. (1989)	contains references to over 6 800 controlled therapeutic studies in perinatal health
Hospital Morbidity Data Base	Mr. Cyril Nair, Chief (613) 951-8387; Mr. Rod Riley, Statistician; Health Care Section, CCHI, Statistics Canada	spontaneous abortion, congenital anomalies, menstrual, hormonal, and reproductive system abnormalities, cancer surgical procedures (ICD)	Gentleman (1991)	data are recorded on an event (separation) basis, not on a person (patient) basis; therefore, not linkable by personal identifiers
Personnel Exposed to Anaesthetic Gases	Sam Guirguis, Ontario Ministry of Labour	spontaneous abortion	Guirguis et al. (1990)	questionnaire results from 8 032 personnel
PCBs in Mothers' Milk	Tom Muir, CCIW; J. Jacobson, Wayne State University	PCBs; congenital abnormalities, childhood development	various	study of infants born to 242 women who ate Lake Michigan fish compared to 71 infants born to mothers who did not eat Lake Michigan fish
1986 Health & Activity Limitation Survey	Statistics Canada	persons with disabilities	The Flett Consulting Group	has been linked with other data bases
IVF Registry	Dr. Arthur Leader, Canadian Voluntary Regulation Association	collected data on each in vitro fertilization (IVF)	The Flett Consulting Group	

	research project comparing perinatal outcome in B.C. and Washington State					
The Flett Consulting Group	The Flett Consulting Group	The Flett Consulting Group	The Flett Consulting Group	The Flett Consulting Group	The Flett Consulting Group	The Flett Consulting Group
clinical characteristics of The Flett Consulting infertile couples Group registered in Canadian health science fertility clinics		rates and frequencies of cancer incidence in Ontario		handicapping conditions, The Flett Consulting including congenital Group anomalies and genetic conditions	all live birth and stillbirth registrations in Canada	declared living births
Dr. John A. Collins, clinical characte Study Chedoke-McMaster Hospital infertile couples (416) 521-2100, ext. 6245 registered in Ca health science f	Dr. Robert Armstrong, Centre for Health Services Policy Research, University of British Columbia (604) 433-4449	Ms. Darlene Dale, Manager rates and frequencies of The Flett Consulting of Operations, Cancer cancer incidence in Group Registration (Ontario), Ontario OCTRF (416) 423-4240	David Bogart, Ontario Ministry of Health (416) 927-7610	Ron Danderfer, Division of Vital Statistics, B.C. Ministry of Health (604) 387-4807	Martha Fair, Statistics Canada (613) 951-1734	Ministère de la santé et des services sociaux du Québec
Canadian Infertility Therapy Evaluation Study (CITES)	British Columbia Perinatal Database	Ontario Cancer Registry	Ontario Health Survey (1990)	British Columbia Health Surveillance Registry	Canadian Birth Data Base (CBDB)	Fichier-maître des naissances du Ministère de la santé et des services sociaux du Québec

Table 3. (cont'd)				
Name of data base	Contact person and organization	Selected exposures or outcomes	Source of information	Features
Canadian Cancer Data Base (CCDB)	Martha Fair, Statistics Canada (613) 951-1734	all cancer incident events occurring in Canada	The Flett Consulting Group	
1. "V. Stats." Vital Statistics 2. Health Surveillance Registry	Ron Danderfer, Division of Vital Statistics, B.C. Ministry of Health (604) 387-4807	death, stillbirth, congenital defects, and selected disability	The Flett Consulting Group	
Chedoke-McMaster Hospitals Labour and Delivery Data Base	Chedoke-McMaster Hospitals		The Flett Consulting Group	
Detailed Claims File	Bill Leach, Ontario Health Insurance Plan (OHIP)		The Flett Consulting Group	

developed by the Flett Consulting Group into categories of probability for record linkage; high, good, fair, or poor. Additional details on the criteria can be found in the child health study (Hayward et al. 1993). The data bases were then cross-tabulated with the specific outcomes and exposures selected in the previous section of this project.

Results

Exposure Data Bases: Response Summary of Questionnaires Relating to Environmental or Occupational Data Bases

Responses were received from 12 of 23 questionnaires sent to the guardians of exposure data bases. The 50 percent response rate can be attributed to the unprecedented nature of the project: it was difficult for people to understand, deadlines did not allow for follow-up telephone calls and validation, and questionnaires sent to private industry became mired in time and corporate constraints.

Only 10 of the responses were sufficiently complete for us to apply the criteria for exposure data bases. Table 4 summarizes the four major record-linkage criteria as applied to these 10 questionnaires. Table 5 shows the record-linkage feasibility according to the exposure of interest. Appendix 2 summarizes the responses to the questionnaires according to the general descriptors referred to above.

Outcome Data Bases: Review of Questionnaires

Responses from the guardians of outcome data bases were received indirectly via the Flett Consulting Group.

The potential subject content of these data bases has been tentatively classified and cross-tabulated in relation to 11 specific adverse reproductive outcomes in Table 6. The major features of these data bases are summarized in Appendix 3.

Conclusion

Our preliminary work on the feasibility for record linkage of the exposure and outcome data bases identified leads us to believe that this is an important and potentially fruitful avenue to explore. Further investigation is needed to evaluate feasibility in greater depth for particular research questions. We can also say that much more information about occupational and environmental exposures is needed. It is our hope that this preliminary work of identification of possible data resources available to answer important questions regarding risks to reproductive health will stimulate researchers in Canada to pursue this approach. There is a wealth of existing data in this country that could be "mined" to produce useful information in this area.

Record-Linkage Assessment Criteria for Exposure Data Bases Table 4.

										1	
	Machine time		z	>	>	z	≨	z	>		٨
	Personnel	z	z	z	>	z	X A	c.	>-		٨
SS	Software		z	٠.	>	z	N A	>	>	Ą	^
Access	Access type	-	٥.	-	z	-	-	Z	Ճ	≨	٨
<	Established policy	>	z	\$	z	z	>	>	>	NA A	٨
	Previous linkage	>	>	z	z	z	¥	z	z	Ą	٨
ſS	Poor or none					×	0	0	0	0	^
Identifiers	Fair			×	×						٨
Ider	Good	×	×								^
Descriptors	əziS	2.8M	1.0M	2 000/ yr.	75 000	35 000	AN	500/Y	2.0M	A A	^
	Time period	51+	30-88	\$	734	\$	NA	77-91	74+	NA	٨
	gniognO	>	>	>	>	>	¥	>	>	NA A	٨
	Coverage %	8	90	100?	95	1-50%	¥	NA	NA A	Ą	٨
	Sample	z	z	z	z	>	¥	>	A N	NA A	^
	Target population	Can	Onl	E	Ont	Ont	Can	Great Lakes	Can	Ą	٨
	Working history	×	×	×	×	×					٨
	əmoɔtuO		×		×						٨
es	sisongsiQ										٨
File roles	Treatment			×							^
	OCC/ENV exposure	×	×			×	×				٨
	OCC/ENV monitoring	×	×			×		×	×	×	NA
Data bases		National Dose Registry for Radiation Workers	Mining Master File	P.E.I. Reproductive Care Database	Ontario Congenital Anomalies Surveillance System	Ontario Hydro	National Registry of Toxic Chemical Residue	Great Lakes Fish Contaminants Surveillance Program	National Air Pollution Surveillance	Aircraft Noise Exposure Forecast	National Work Injuries Statistics Program

Table 5. Potential Relevant Content of Exposure Data Bases

	DBCb		٠	•		~	C				c.	0.	c.	×	•	
st	Solvents		•	•	100	0	c.		~		×	×	×	×	•	
of interest	nixoiQ	<i>y</i>	٠	•		<i>ر.</i>	c-		c.		×	×	×	C	•	
	Carbon monoxide		0	•		~	c.		c.		×	•	•	c.	•	
Exposure	Гезд		٠	•		c.	c.		c.		×	×	×	×	•	
Expo	Temperature		•	•		~	c.		×		×	•	•	•	•	
	əsioN		•	•		c.	c.		×		×	•	•	•	×	
	noitsibsA		×	×		c·	c.		×		×	•	•	•	•	ı
Name of data base		High Record-Linkage Potential	National Dose Registry for Radiation Workers	Mining Master File	Good Record-Linkage Potential	Ontario Congenital Anomalies Surveillance System	PEI Reproductive Care	Poor Record-Linkage Potential	Ontario Hydro Industrial Hygiene Laboratory Exposure Records	Unlikely Record-Linkage Potential	National Work Injuries Statistics Program	National Registry of Toxic Chemical Residues	Great Lakes Fish Contaminants Surveillance Program	National Air Pollution Surveillance	Aircraft Noise Exposure Forecast	

Table 6. Potential Relevant Content of Outcomes Data Bases

	Childhood development		•	•	•	•	c·	ć	6	•	•		c
	Childhood cancer		•	•	5	×	خ	×	×	•	•		5
	Congenital anomalies		•	•	5	•	٠	×	×	•	<i>٠</i>		٠-
est	Low birthweight		•	•	5	•	ç.	×	×	•	×		c.
Outcomes of interest	Ahidlita		×	×	×	•	<i>~</i>	×	×	×	×		c-
s of	Toxemia (pre-eclampsia)		•	•	×	•	ċ	×	×	•	×		C
ome	Spontaneous abortion		c-	c.	×	•	٠	×	×	•	×		c.
Onto	Abnormalities of the sivies		•	•	٠.	•	<i>ا</i>	×	×	•	خ		c.
	Hormonal disorders (male and female)		•	•	ć	•	٠	×	×	•	ç		c·
	Spermatogenesis disorders		•	•	<i>د</i> .	•	6	×	×	•	٠.		ç.
	Menstrual disorders				٠.	•	٠٠	×	×	•	٠.		٠.
Name of data base		High Record-Linkage Potential	Integrated Vital Statistics Data Base (IVS)	Canadian Mortality Data Base	Nova Scotia Perinatal Data Base	Ontario Cancer Registry (OCR)	OHIP Detailed Claims File	Manitoba Permanent Medical Statistical File	British Columbia Health Surveillance Registry	Canadian Birth Data Base (in preparation)	Prince Edward Island Perinatal Data Base (in preparation)	Good Record-Linkage Potential	Ontario Health Survey (OHS)

	フィロフン	
•	2	ċ
	g	2
	9	2

	Childhood development		ŀ	c	0	0	•	×	•		·	×		•	•	T ·
	Childhood cancer		•	C	0	×	•	×			•	×		•	•	>
	Congenital anomalies		•	0	×	×	×	×	· C.		c.	×		c.	0	ļ
est	Low birthweight		•	•	C	×	0	•	c.		~	•		~	0.	1
inter	Stillbirth		•	•	×	×	×	•	×		٠.	•		c.	0	,
s of	Toxemia (pre-eclampsia)		٠	•	•	×	C	•	0.		2	•		<i>ر</i> .	c.	•
Outcomes of interest	Spontaneous abortion	1	•	•	~	×	×	•	0		٠.	•		~	c.	•
Outc	Abnormalities of the cervix			•	•	×	٥.	•	c.		c.	•			c.	•
	Hormonal disorders (male and female)		•	•	•	×	c.	•	c.		¿	•			~	•
	Spermatogenesis disorders		•	•	•	×	c	•	c.		×			•	c.	
	Menstrual disorders					×	C.		0.		×			2	c.	
Name of data base		Possible Record-Linkage Potential	Census of Canada (Series B)	1986 Health and Activity Limitation Survey	Canadian Congenital Anomalies Surveillance System	Hospital Medical Records Institute (HMRI)	IVF Registry	Ontario Child Health Study and Follow-up	British Columbia Perinatal Data Base	Poor Record-Linkage Potential	Canadian Infertility Therapy Evaluation Study	Easter Seal Client Registry	Unclassified Record-Linkage Potential	Chedoke-McMaster Hospitals Labour and Delivery Database	Fichier maître des naissances du Ministère de la santé et des services sociaux du Québec	Canadian Cancer Data Base

Appendix 1. Letter and Questionnaire

April 16, 1992

Dear

Thank you for your interest in the enclosed questionnaire. As discussed, this questionnaire is part of a project exploring The Linkage Potential of Occupational and Environmental Data to Adverse Reproductive Data in Canada. This project is sponsored by The Royal Commission on New Reproductive Technologies. The project aims at identifying the availability of data bases that could be used in record linkage studies.

In this project, we have worked in cooperation with the Flett Consulting Group who prepared most of the questionnaire. We have added the specific questions dealing with occupational and environmental data bases. The responses will be tabulated and analyzed in a final report. When completed, this report will catalogue exposure and outcome data bases relevant to the Commission's concern to improve understanding of the cause and prevention of adverse reproductive outcomes.

Because of the tight deadlines of the Royal Commission, we would appreciate it if you could complete the questionnaire and return it by April 24, 1992. Please use the enclosed return envelope and send by courier to CCOHS collect or fax to (416) 572-2206.

Again, thank you for your cooperation. If you have any questions about the study or the questionnaire, please call me or Ruth Parr (416) 572-4525. We look forward to hearing from you shortly.

Yours sincerely

L.M. Tennassee, M.D. Chief Medicine, Toxicology and Ergonomics

THE LINKAGE POTENTIAL OF OCCUPATIONAL AND ENVIRONMENTAL DATA TO ADVERSE REPRODUCTIVE DATA IN CANADA STUDY QUESTIONNAIRE

Royal Commission on New Reproductive Technologies

The purpose of this questionnaire is to gather information that will help us assess the record-linkage possibilities of relevant Canadian data bases for The Linkage Potential of Occupational and Environmental Data to Adverse Reproductive Data project conducted by the Royal Commission on New Reproductive Technologies. Your assistance is greatly appreciated. Please circle the appropriate answer or print your response in the space provided. If you have any questions, please call Dr. Maritza Tennassee, the project manager, or Ruth Parr at (416) 572-4525. When you have completed the questionnaire, please return it to us by courier collect or by fax (416) 572-2206. Thank you.

First, we would like to ask you a few general questions about the data base.

1.

a)	Ha	s this data base been known by any other names?
	1	yes Please list
	2	no

	ere is the data base physically loc vince.	ated? Please indicate city and
	city	province
Brie	efly, describe purpose for which th	is data base was designed.
Wha geog	at is the target population for the graphical area, demographic char	ne data base? Please indicate acteristics, gender, etc.
a)	Are any groups excluded from residing in institutions or living	the sample, such as persons on reservations, etc.?
	1 yes Please describe	
	2 no	
Is t	the data collected for a sample?	
1 2.	yes no (GO TO Q7)	
a)	If yes, approximately what prosampled?	portion of the population was
1_ \	Is a sighting assured to make the	as comple representative?
b)	Is weighting required to make the	le sample representative:

%

7. What is your overall response rate? __

8.	Are	there any known biases in the coverage of the population?
	1	Yes Please explain
	2	No
9.		general, what proportion of the target population is included in the al data base?
		%
10.	Wo	uld you say this data is (PLEASE CIRCLE ALL THAT APPLY)
	1 2	a one-time, cross-sectional survey a longitudinal survey which follows the same group of respondents over a period of time
	3	a repeated survey with different respondents each time, such as an annual study to monitor the public awareness of a health promotion program
	4	or an ongoing data collection process which is updated as each new event occurs
FA	ONI	E-TIME SURVEY, PLEASE GO TO Q12.
11.	Wh	at is the frequency of collection? Is it
	1	variable (GO TO Q12)
	2	at regular intervals
	a)	If at regular intervals, would this be
		 weekly monthly semi-annual annual some other interval Please specify
	b)	Approximately how many records are added each time?

	c)	Is there a planned completion date, for example, a five-year study ending in 1993?
		1 yes When will that be? Month Year
		2 no
12.		nere a limited period over which the data will be retained, for nple, five years?
	1	yes Please specify
	2	no .
13.	For	what time period is the data presently available?
	Fron	m to
14.	App	roximately, what is the size of the data base?
		records per year, or records in total
		t few questions deal with technical characteristics of the data ch are important in assessing the feasibility or record linkage.
15.	How	v is this data base stored?
	1 2 3	in machine-readable form as raw data (i.e., ASCII) in a software-defined data base (i.e., a SAS or dBase data base) in some other form Please describe
16.	Is th	ne unit of analysis
	1 2 3	individual (i.e., a case history, with one record per individual) family (i.e., a family history, family registration) event (i.e., doctor visits, with varying numbers of records per individual) or something else (i.e., number of procedures performed). Please explain

- 17. Has this data base been linked to other data bases?
 - 1 yes
 - 2 · no ... (GO TO 918)
 - a) If yes, which data bases have been linked? Please list.

The question below concerns the presence of identifying variables which could be used to link records across data bases. We realize that each data base has necessary confidentiality concerns associated with these variables. At this time we are not asking about the availability of this information per se, rather we are trying to assess the <u>technical</u> possibility of linkage.

18. For each identifying variable listed could you please check in the appropriate column if it is retained in machine-readable or some other form (i.e., a list), and note approximately what proportion of the records in the data base contain information for this variable. For example, the data base may have a field for nickname, however only 10% of the records had individuals with nicknames.

		Retair	Percentage of records in	
	Identifying variable	machine- readable form	some other form	which variable is found
1.	surname			
2.	alternate surname ever used			
3.	first given name			
4.	first initial			
5.	second given name			
6.	second initial			
7.	usual name or nickname			
8.	sex			

		Retair	Percentage of records in which	
	Identifying variable	machine- readable form	some other form	variable is found
9.	marital status			
10.	year of birth			
11.	month of birth			
12.	day of birth			
13.	birth province or country			
14.	birth city or place			
15.	father's surname			
16.	father's first given name			
17.	father's first initial			
18.	father's second given name			
19.	father's second initial			
20.	father's birth province or country			
21.	mother's maiden name			
22.	mother's first given name			
23.	mother's first initial			
24.	mother's second given name			
25.	mother's second initial			
26.	mother's birth province or country			
27.	own place of residence (province or country)			
28.	own place of residence (city/town)			
29.	postal code			

		Retair	Percentage of records in	
	Identifying variable	machine- readable form	some other form	which variable is found
30.	last known year alive			
31.	year of death			
32.	month of death			
33.	day of death			
34.	place of death (province or country)			
35.	place of death (city/town)			
36.	Social Insurance Number			
37.	Death Registration Number			
38.	Health Insurance Number			
39.	Other identifying numbers, please specify			
40.	Other identifying variables, please specify			

9.	Is this data	base sorted	by	any	of	the	above	identifying	variables?
----	--------------	-------------	----	-----	----	-----	-------	-------------	------------

1	yes Which?		

2 no

2

no

1. position, job title

The next few questions deal with occupation and environment.

20. Does the data include information on occupation?

		1 2	yes no
	2.	leng	th of employment
		1 2	yes no
	3.	type	of work
		1 2	yes no
	4.	prev	ious work history
		1 2	yes no
	5.	othe	er information — please list
21.		s the	e data base include information on any aspect of the
	1.	type	of exposure
		1	yes please specify
		2	no
	2.	type	e of monitoring
		1	yes please specify

3.	oth	er information please specify
	1	yes please specify
	2	no
Do	es th	ne data base include information on any aspect of the nent?
1.	air	samples
	1	yes please specify
	2	no
2.	soil	samples
	1	yes please specify
	2	no
3.	wate	er samples
	1	yes please specify
	2	no

22.

556 l	Inderst	anding	Infertility
	4.	othe	r information
		1	yes please specify
		2	no
The		few (questions deal with requirements for access to this dat
23.	Have	e you data	established a policy and procedure for record linkage with base?
	1 2	yes no	Is there any particular reason?
24.	Brie wish	fly dened to	escribe what the application process would involve if someon o link the records in this data base to another data base.
25.			e specific restrictions on who would be eligible to apply for nkage?
	1 2	yes no .	(GO TO Q23)
	a)	If ye	es, please explain

- 26. Would an applicant have direct or indirect access to the data base?
 - 1 direct (i.e., could link at applicant's site)
 - 2 indirect (requests would be handled by you)
 - 3 negotiated
 - 4 no access given for record linkage ... (GO TO Q27)

27. Do you have the facilities (software, machine time, and personnel) available to do record linkages at your site?

a)	software, specify	yes 1	no 2
b) c)	machine time experienced personnel	1	2 2

- 28. With regard to the costs an applicant could expect when linking to your data base, do you ...
 - 1 have a fee schedule
 - 2 prepare a quote for each request
 - 3 or something else? Please explain ...

Appendix 2. Response Summary of Questionnaires Relating to Environmental or Occupational Data Bases

The National Dose Registry for Radiation Workers

(Bureau of Radiation and Medical Devices, Health and Welfare Canada, 775 Brookfield Road, Ottawa, Ontario, K1A 1C1)

General Characteristics

Purpose:

• radiation epidemiology; regulatory control of radiation workers; statistical analysis of dose trends; legal purposes — e.g., evidence of exposure for compensation

Target Population: Coverage:

• entire population of monitored workers in Canada

response rate n.a.no known biases

 estimated proportion of the target population included is about 99 percent

Data Collection:

 an ongoing data collection process updated at regular intervals: semi-monthly, monthly, quarterly, annually (an average of 4.2 records

added each time)

Time Period:

• data are available 1951 to present, with 80-year retention period

558 Understanding Infertility

Size:

• approximately 140 000 records a year and 280 000 records in total

Unit of Analysis:

• individual, with many records for each individual; and annual summary for each individual by place of monitoring and type of radiation

Technical Characteristics

Data Storage:

• in IMAGE DATABASE

Previous Record

Linkage:

 has been linked to Canadian National Mortality Data Base (Statistics Canada)

Identifying Variables (approximate percentage of records):

• surname (100 percent)

• alternate surname

• first given name (44 percent)

• first initial (98 percent)

• second given name (16 percent)

• second initial (26 percent)

• sex (87 percent)

• year of birth (85 percent)

• month of birth (84 percent)

• day of birth (84 percent)

• birth province or country (35 percent)

• father's first given name (ca. 1 percent)

 mother's maiden name (ca. 1 percent) • social insurance number (82 percent)

place of employment (100 percent)

Occupational or Environmental Information

Occupational:

· position, length of employment, type of work, previous work history

Workplace Exposure: • radiation, external and internal tritium, radon daughter estimates

Workplace Monitor: Environment:

• gamma, x-ray, beta, neutron, tritium, alpha • air samples (radon daughter estimates)

Access

Policy:

· established policy and procedure

Procedure:

· requests should be submitted with research proposal to the Head, National Dose Registry Section, Bureau of Radiation and Medical Devices. The registry is a federal data bank covered by the Privacy Act. Access must be in terms of this act.

Type of Access:

· indirect, handled by Bureau of Radiation and Medical Devices

Resources Available: • software

(powerhouse), machine time, and

personnel

Costs:

 quote prepared for each request on a cost-recovery basis

Contact Person:

• Dr. Pat Ashmore, Health and Welfare Canada (613) 954-6660

Mining Master File

(Statistical Unit, Health and Safety Policy Branch, Ontario Ministry of Labour, 400 University Avenue, 8th Floor, Toronto, Ontario, M7A 1T7)

General Characteristics

Purpose:

· to study the mortality rates in Ontario miners

Target Population:

· men who worked in Ontario mines after 1954, excluding those who did not work for 60 months

Coverage:

• response rate 100 percent

· no known biases

· estimated proportion of the target population included is about 100 percent

Data Collection:

· a longitudinal survey that follows the same group of respondents over a period of time but with data collected at regular annual intervals

Time Period:

· data are available from 1930 to 1988

Size:

· thousands of records are added each year, and the size is about 1 000 000 records in total

Unit of Analysis:

· individual case history, with one record for each individual

Technical Characteristics

Data Storage: Previous Record • in machine-readable form as raw data: ASCII

Linkage:

· has been linked to Canadian National Mortality Data Base (Statistics Canada) and Income Tax Files

Identifying Variables (approximate percentage of records):

- surname
- alternate surname
- first given name
- first initial
- second given name
- second initial
- sex
- · year of birth
- month of birth
- · day of birth

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- birth province or country
- · last known year alive
- year of death
- · month of death
- · day of death
- place of death (province or country)
- social insurance number
- · death registration number
- · miner's certification number

Occupational or Environmental Information

Occupational:

· length of employment, type of work, previous work history (only if it was mining)

Workplace Exposure: • separate hard-copy information exists about the job in the particular mine

Workplace Monitor:

radon decay products

Environment:

• there are no data on air, soil, water, or other environmental samples

Access

Policy:

no policy has been established

Procedure:

 requests should be submitted along with description of the project and its purpose. Freedom of information and protection of personal privacy apply to these data

Type of Access:

• respondent does not know

Resources Available:

· no software; machine time and personnel are available

Costs:

respondent does not know

Contact Person:

• Dr. Sam Guirguis, Chief, Health and Safety Studies, Ontario Ministry of Labour (416) 326-7882

PEI Reproductive Care Data Base

(PEI Reproductive Care Program Inc., PEI Department of Health, 559 North River Road, Charlottetown, PEI, C1E 1J7)

General Characteristics

Purpose:

- to monitor effects of intervention programs
- to provide morbidity and mortality statistics for perinatal period

Target Population:

• pregnant women who live in PEI

Coverages:

- response rate 100 percent no known biases
- theoretical proportion of the target population included is 100 percent

Data Collection:

 an ongoing data collection process that is updated as each new event occurs for an unlimited projected period of time

Time Period:

 data are available from 1988 to the present but in manual form only

Size: Unit of Analysis: approximately 2 000 records are added each year
individual case history, with one record for each individual

Technical Characteristics

Data Storage:

• manual at present, but in the near future in machine-readable form as raw data: ASCII

Previous Record

Linkage:

• there is no history on linkage to other data bases

Identifying Variables (approximate percentage of records):

• surname (100 percent)

• first given name (100 percent)

• second initial (100 percent)

• sex (100 percent)

• marital status (100 percent)

year of birth (100 percent)month of birth (100 percent)

• day of birth (100 percent)

• own place of residence — province or country (100 percent)

• own place of residence — city/town (100 percent)

• postal code (100 percent)

• social insurance number (100 percent)

• health registration number (100 percent)

• other number — prenatal record number (100 percent)

Occupational or Environmental Information

Occupational:

position/job title, type of work

Workplace Exposure: • there is no information on type of exposure or type of monitoring

Environment:

 there are no data on air, soil, water, or other environmental samples

Access

Policy:

 no policy has been established but one is being planned

Procedure:

• restrictions are expected but procedure is in the planning stage

Type of Access:

• indirect, handled by the guardians

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Resources Available:

no software yet but expected; machine time is

available but no experienced personnel

Costs:

· unknown at this time

Contact Person:

• Ms. Maida MacCallum, PEI Reproductive Care Program Inc.

Ontario Congenital Anomalies Surveillance System

(Public Health Promotion Service, Public Health Branch, Ontario Ministry of Health, 5th Floor, 15 Overlea Boulevard, Toronto, Ontario, M4H 1A9)

General Characteristics

Purpose:

- to establish incidence of congenital anomalies
- to monitor variations in incidence

Target Population:

· all newborns born in Ontario with congenital anomaly(ies) identified at birth or within one year after birth

Coverage:

- response rate 95-98 percent
- · as data rely on reports by physicians and hospitals, biases may result. Missed cases are not reported
- · theoretical proportion of the target population included is 95 percent

Data Collection:

· an ongoing data collection process, updated as each new event occurs for an unlimited projected period of time

Time Period:

· data are available from 1973 to the present

Size:

· approximately 4 000 records are added each year to approximately 75 000 records in total

Unit of Analysis:

• individual case history, with one record for each individual

Technical Characteristics

Data Storage:

- in machine-readable form as raw data: ASCII
- also in software-defined data base

Previous Record

Linkage:

there is no history on linkage to other data bases

Identifying Variables (approximate percentage of records):

- sex (100 percent)
- year of birth (100 percent)
- month of birth (100 percent)
- day of birth (100 percent)
- birth province or country (?)
- birth city or place geographical code (90 percent)
- postal code (80+ percent since 1984)
- month of death within first year of life

- day of death
- health insurance number (90+ percent)
- other number prenatal record number (100 percent)

Occupational or Environmental Information

Occupational:

• some data but not all on position/job title

Workplace Exposure: • there is no information on type of exposure or type of monitoring

Environment:

• there are no data on air, soil, water, or other environmental samples

Access

Policy:

· no policy has been established

Procedure:

• requires permission from Hospital Medical Records Institute

Type of Access:

negotiated

Resources Available:

• software, machine time, and experienced personnel are available

Costs:

· unknown at this time

Contact Person:

• Dr. Roch Khazen, Public Health Promotion Service (416) 327-7376

Ontario Hydro Industrial Hygiene Laboratory Exposure Records

(Human Resources Branch, 757 McKay Road, Pickering, Ontario, L1W 3C8)

General Characteristics

Purpose:

• to capture employee exposure measurements to hazardous agents performed by industrial hygiene laboratory

Target Population:

• employees of Ontario Hydro

Coverage:

• variable from 1 to 50 percent at various work locations

· biases may result as data reflect worst-case situations

proportion of the target population is unknown

Data Collection:

· an ongoing data collection process, updated at variable intervals as each new event occurs for an unlimited projected period of time

Time Period:

• data are available from 1985 to the present (some are available back to 1980)

Size:

• approximately 5 000 records are added each year to approximately 35 000 records in total

Unit of Analysis:

• number of exposure measurements performed

Technical Characteristics

Data Storage: • in a software-defined data base

Previous Record

Linkage: • there is no history on linkage to other data bases

Identifying Variables (approximate percentage of records):

• surname

- first given name
- · first initial
- also trade
- also work location

Occupational or Environmental Information

Occupational: • data include position/job title and type of work

Workplace Exposure: • type of exposure is recorded by agent; type of monitoring includes personal and area for

specified measurement periods

Environment: • personal and area air samples are recorded

Access

Policy: • no policy has been established

Procedure: • requires permission from the director of the Health

and Safety Division

Type of Access: • indirect through the company

Resources Available: • no software, machine time, or experienced

personnel are available for record linkages

Costs: • no comment

Contact Person: • Dr. Steven Libich, Supervisor, Industrial Hygiene

Laboratory Service (416) 683-7516

National Registry of Toxic Chemical Residues

(Environment Canada, Canadian Wildlife Service, National Wildlife Research Centre, 100 Gamelin Blvd., Hull, Quebec, K1A 0H3)

General Characteristics

Purpose: • to monitor toxic chemical residue levels in wildlife

in Canada

Target Population:
• contains data on toxic residues in wildlife in Canada, including the Great Lakes region; no

human data are included in the data base

Coverage: • n.a. Data Collection: • n.a.

Time Period: • n.a. Size: • n.a.

Unit of Analysis: • n.a.

Technical Characteristics

Data Storage:

n.a.

Previous Record

Linkage:

• n.a. - the data base has been used in other health studies to provide indicators of the health of the environment

Identifying Variables (approximate percentage of records):

- · geographical area
- species of wildlife · chemical of concern
- year of collection
- etc.

Occupational or Environmental Information

Occupational:

• n.a.

Workplace Exposure: • n.a.

Environment:

• wildlife samples — birds, fish, mammals

Access

Policy:

established policy exists for record linkage

Procedure:

· a handwritten request must be presented; all information in the data base is subject to review and comment by the Canadian Wildlife Service before release in a final document

Type of Access:

· indirect through the owner

Resources Available: Costs:

• n.a. n.a.

Contact Person:

• Mr. Jim Learning, Canadian Wildlife Service (819) 997-6122

Great Lakes Fish Contaminants Surveillance Program

(Ecotoxicology Division, Great Lakes Laboratory for Fisheries and Aquatic Sciences, Fisheries and Oceans Canada, Bayfield Institute, 867 Lakeshore Road, P.O. Box 5050, Burlington, Ontario, L7R 4A6)

General Characteristics

Purpose:

• to determine spatial and temporal trends of toxic chemicals in Great Lakes fish

Target Population:

• Great Lakes fish - Ontario, Erie, Huron, and Superior (lake trout and rainbow smelt)

Coverage:

• n.a.

Data Collection:

· a repeated annual survey with different samples each time involving 50 fish per species per year from eight or nine different sites

Time Period:

· data are available from 1977 to 1991

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Size: • approximately 500 records are added each year

Unit of Analysis: • number of exposure measurements performed

Technical Characteristics

Data Storage: • in a software-defined data base

Previous Record

Linkage: • there is no history on linkage to other data bases

Identifying Variables: • n.a.

Occupational or Environmental Information

Occupational: • n.a. Workplace Exposure: • n.a.

Environment: • biological data

Access

Policy: • access policy has been established

Procedure:
• requires joint authorship for accredited research publication by an accredited professional research

program

Type of Access: • indirect and negotiated through the company

Resources Available: • software is available, but not machine time or experienced personnel

Costs: • quote is required for each request

Contact Person: • D.M. Whittle, Manager, Ecotoxicology Division,

Great Lakes Laboratory for Fisheries and Aquatic

Sciences (416) 336-4565

National Air Pollution Surveillance

(Environment Canada, Conservation and Protection, Pollution Measurement Division, Technology Development Branch, River Road Environmental Technology Centre, 3439 River Road, Ottawa, Ontario, K1A 0H3)

General Characteristics

Purpose: • to maintain data on air pollutants from urban

areas to examine for trends

Target Population: • Canadian urban centres

Coverage: • n.a

Data Collection: • an ongoing data collection of hourly averages

updated monthly for an unlimited projected period of time

Time Period: • data are available from 1974 to the present

Size:
• approximately 100 000 records are added each year to approximately 2 000 000 records in total

Unit of Analysis: • hourly pollutant concentrations

Technical Characteristics

Data Storage:

• in a software-defined data base

Previous Record

Linkage:

• there is no history on linkage to other data bases

Identifying Variables (approximate percentage of records):

- city/site pollutant
- date

Occupational or Environmental Information

Occupational:

• n.a.

Workplace Exposure: • n.a.

Environment:

· air samples: sulphur dioxide, carbon monoxide, nitrogen dioxide, ozone, particulate matter, lead sulphate, and lead nitrate

Access

Policy:

· established policy for access exists

Procedure:

· application is possible through the owner (Environment Canada) and by computer account at the Toronto site: there are no restrictions on the use of a linked file or released information

Type of Access:

· both direct access at the applicant's site and indirect access through the owner are possible

Resources Available:

• software, machine time, and experienced personnel are available

Costs:

· quotes are required for each request

Contact Person:

• John Shelton, Supervisor, NAPS Data Publications Unit, Ambient Measurement Section (613) 991-9453

Aircraft Noise Exposure Forecast

(Transport Canada, Tower C, 7th Floor, Place de Ville, 330 Sparks Street, Ottawa, Ontario, K1A 0N8)

 nothing on the questionnaire was considered applicable

Contact Person:

• Gilles Bourgeois, Transport Canada (613)991-9981

National Work Injuries Statistics Program

(National Work Injuries Statistics Program, Jean Talon Building, 7th Floor, Tunney's Pasture, Ottawa, Ontario, K1A 0T6)

- Most of the questionnaire was considered non-applicable because:
- the information is considered confidential
- the data do not contain any identifiers

Contact Person:

• Joanne Proulx, Chief, National Work Injuries

Statistics Program (613) 951-4046

Appendix 3. Review of Questionnaires of Outcomes Data **Bases Received from Flett Consulting Group**

The Flett Consulting Group prepared a questionnaire that assesses the linkage potential of over 20 outcomes data bases. We received copies of these questionnaires from Flett, and extracted some brief information on the data bases' purpose and content, which is summarized here.

Data Bases with High Record-Linkage Potential

Integrated Vital Statistics Data Base (IVS)

- covers recorded events of live births, stillbirths, marriages, and deaths in Canada:
- purpose is to produce aggregate numbers and rates of births, marriages, and deaths for Canada and provinces and provide related vital statistics for information use by federal, provincial, and other agencies.

Canadian Mortality Data Base (CMDB)

- covers all death events occurring in Canada or United States for Canadian residents:
- for national historical mortality record linkage studies, epidemiology studies, and generation of other statistical products;
- includes cause of death, nature of injury, place of injury, pregnancy death, operation, autopsy, autopsy findings, kind of work done (occupation), kind of industry;
- also includes immediate cause of death, place of death, location name, antecedent cause leading up to death (ICD-9).

Nova Scotia Perinatal Data Base

- purpose is to record clinical audit and research of perinatal events in Nova Scotia:
- includes baby's status (live born or stillborn).

Ontario Cancer Registry (OCR)

purpose is to provide statistics on the rates and frequencies of cancer incidence for the province of Ontario;

- to provide a data base for epidemiological research in cancer;
- covers all cancer patients in Ontario.

OHIP Detailed Claims File

- examine trends in payment claims (which reflect the income levels of physicians who send bills to OHIP) and trends of specific types of patients who use OHIP;
- covers the entire population of Ontario.

Manitoba Permanent Medical Statistical File

- purpose is to provide a permanent statistical record of insured medical services by health care practitioners and to generate payments to providers of these services;
- it covers all persons legally entitled to remain in Canada and who are permanent residents of Manitoba;
- it records doctor visits.

British Columbia Health Surveillance Registry

- an active file of congenital defects and selected disabilities;
- purpose is to locate and verify personal vital event data for the issuance of certificates and also for research on natality, mortality, fertility, health status, mapping, etc.;
- covers the entire province of British Columbia; includes all events;
- includes ICD-9 codes, hospital, autopsy, disposition, birthweight, gestation, cause of death, and occupation.

Canadian Birth Data Base (data base currently in preparation)

- will be constructed from data from the Integrated Vital Statistics System (including live births and stillbirths); the data will be prepared in a format suitable for record linkage;
- purpose is for national historical record linkage and epidemiological studies;
- will include all live birth and stillbirth registrations occurring in Canada.

Prince Edward Island Perinatal Data Base (currently in preparation)

• purpose is to provide information or statistics on perinatal morbidity/mortality, lifestyle factors, intervention programs on outcome data (such as length of pregnancy and birthweight).

Data Bases with Good Record-Linkage Potential

Ontario Health Survey (OHS)

- · goal and objectives not received;
- includes residents of private dwellings in Ontario from January to November 1990.

Data Bases with Possible Record-Linkage Potential

Census of Canada (Series B)

- Series A covers 100 percent; Series B covers 20 percent;
- includes occupation and industry in Series B for people in the labour force.

1986 Health and Activity Limitation Survey — Children

- purpose is to gather information on barriers faced by persons with disabilities in their daily activities;
- the target population is children living in households.

Canadian Congenital Anomalies Surveillance System (CCASS)

- purpose is for basic surveillance, in a passive sense, of birth defects in Canada;
- it covers all births in hospitals affiliated with the Hospital Medical Records Institute plus the Province of Manitoba.

Hospital Medical Records Institute (HMRI)

- includes inpatient data base and day surgery data base;
- purpose includes administrative data base for hospital management purposes and creation of provincial morbidity data bases;
- includes discharges from HMRI hospitals (primarily acute care inpatients and day surgery visits).

IVF Registry

- purpose is to collect case data on IVF attempts in Canada, including outcome of treatment, normality of infants, and morbidity;
- includes Canadian consumers, the IVF clinics in Canada, the medical profession, health professionals, government policy makers;
- covers only people undergoing treatment;
- only half of the clinics in Canada contribute data.

Ontario Child Health Study and Follow-up

- purpose was to study the epidemiology of childhood psychiatric disorders, physical health, and substance use in Ontario children;
- includes households with children aged 4 to 16 years in 1983.

British Columbia Perinatal Data Base

- purpose involves a research project comparing perinatal outcome in British Columbia and Washington State — B.C. data from 1986 to 1989;
- it includes all births in British Columbia during this period;
- it has linked vital statistics, medical services, and hospital programs.

Data Bases with Poor Record-Linkage Potential

Canadian Infertility Therapy Evaluation Study

- research data base to determine the distribution of clinical characteristics of infertile couples registered in Canadian health science centre infertility clinics and to evaluate the treatment given and outcome during 36 months following registration (follow-up extended to cover 1988-1991 for 75 percent);
- includes infertile couples with a complaint of infertility of more than 12 months' duration who contacted one of 10 participating university clinics.

Easter Seal Client Registry

- purpose is to provide the Easter Seal Society with a more adequate picture of the children on its active case load, in particular to highlight the principal characteristics of the new and active cases to provide a profile of the needs for specialized services;
- covers persons on the active case load of the Easter Seal Society

 persons living within Ontario under the age of 19 years whose restriction of activity by reason of neurological, musculoskeletal, or other organic defects produces a physical handicap.

New Questionnaires Not in Flett's Early Draft

Chedoke-McMaster Hospitals Labour and Delivery Database

 purpose is to monitor labour and delivery activity; monitor indicator rates, such as rates of Caesarian section, episiotomy, etc.; and provide background data on planning research studies; • it covers regional referrals delivering at tertiary centres and community deliveries at McMaster.

Fichier maître des naissances du Ministère de la santé et des services sociaux du Québec

• the purpose is to declare living births in Quebec.

Canadian Cancer Data Base

- file was constructed as a linkable data base from the National Cancer Incidence Reporting System, Statistics Canada;
- the purpose is for national, historical cancer incidence recordslinkage studies and epidemiology studies involving all cancer incident events occurring in Canada;
- information includes a list of descriptors that include ICD-9 code and ICD-8 code, but no specific occupational information seems to be included.

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Evaluation of an Environmental Contaminant: Development of a Method for Chemical Review and a Case Study of Hexachlorobenzene (HCB) as a Reproductive Toxicant

John F. Jarrell, Judy Seidel, and Philip Bigelow



Executive Summary

An extensive literature review was undertaken to identify what links have been made, and how they have been made, between hexachlorobenzene (HCB) and infertility. The selection of HCB for review was based mainly on its persistence in the environment and its known severe toxicity at high concentration.

Major adverse reproductive effects have been reported from HCB exposure. The gonads appear to be particularly affected, but placental and lactational transfer of HCB to the fetus and neonate, respectively, is also highly relevant to the health of the offspring. In this regard, the tissue burden data indicate that a steady decrease has occurred in recent years in Canada in the levels of HCB found in all tissue types in both animals and humans.

A case-control study is the second focus of this report. The reproductive performance of a sample of in vitro fertilization (IVF)

This paper was completed for the Royal Commission on New Reproductive Technologies in November 1992.

patients who had had previous follicular fluid sampling for HCB and, for comparison, a group who had had polychlorinated biphenyl (PCB) and dichlorodiphenyldichloroethylene (DDE) sampling was studied. Interpretation of the data is not easy. The fact that PCB levels are considerably higher among infertile women with no pregnancies than among those with prior pregnancies suggests that an anti-fertility effect of PCBs cannot be excluded. However, the lower levels of HCB in the serum and follicular fluid of women with a prior pregnancy may be the result of HCB transfer out of the woman's body system to the fetus. The results must therefore be interpreted carefully, since several hypotheses may explain or partially account for the finding.

Based on the results of this study,* the following measures can be recommended:

- 1. Support the monitoring of human ovarian follicular fluid for priority chemicals to further establish normative data, and collect data on prior reproductive events in these women, through continual review of patients receiving IVF.
- 2. Support the monitoring of serum PCBs with the purpose of evaluating any relation to infertility using appropriate epidemiologic study.
- 3. Support the appropriate use of animal studies to assess the mechanism of action of such ovarian toxicants.
- 4. Support the reporting by regulatory agencies of the concentrations (by categories) of priority organochlorines, along with information on prior reproductive experience and breast-feeding history.

Introduction

Whether human reproductive systems are harmed when exposed to environmental chemical agents has been of increasing concern; over the past decade, numerous authors have written about possible links between chemical exposure in both work and everyday living environments and declining fertility. This concern has identified the need for both animal and human data and information on chemical agents with unknown or suspected adverse actions on all aspects of reproduction — from healthy reproductive organs to the likelihood of conception and the delivery of healthy children.

Much research has been conducted into the carcinogenic effects of environmental chemical agents on human and animal health. However, there is a definite lack of research directed specifically at the effects of such

^{*} This document is a summary version containing the text, essential tabular information, and some applicable references. A longer version with over 1 400 references and additional appendices is available from the archives of the Royal Commission on New Reproductive Technologies.

chemicals on reproductive health. Also apparent is that the release of most chemicals into the environment is not controlled or regulated on the basis of adverse actions that the chemicals might have on reproduction (Chelimsky 1991).

Hexachlorobenzene (HCB) is the chemical selected for review in this study. Its selection is based primarily on its remarkable persistence in the environment and severe toxicity at high concentration. The selection of HCB does not imply that investigating other chemical agents with regard to adverse reproductive consequences is not important. A thorough investigation of chemicals such as polychlorinated biphenyls (PCBs), dichlorodiphenyldichloroethylene (DDE), dibenzodioxins, and dibenzofurans is equally important and requires future studies to evaluate the relationship between these agents and their adverse reproductive effects.

HCB was originally introduced as a fungicide to control seed wheat smut in 1946. In the late 1950s, a large Turkish population was accidentally exposed to large amounts of HCB by consuming cereal products produced from HCB-treated grain. Since then, the toxicity of HCB has been intensively researched, but the mechanisms of toxicity are not yet clearly understood. In sufficient concentrations, HCB produces many toxic effects, hepatic porphyria being the major outcome investigated. HCB has been banned from use as a fungicide in North America since the late 1970s, but exposures still occur because it is produced as a by-product in the manufacture of chlorinated solvents and pesticides and other industrial processes. Its continued production, bioaccumulation, and persistence indicate a need to assess its effects on reproduction.

Objectives

A comprehensive literature review is the first step in providing evidence on what links have been made, and how they have been made, between HCB and infertility. The first objective was therefore to conduct a literature review that contributes to our understanding of the effects of HCB on male and female reproduction, specifically its effects on fertility. The literature review provides an essential basis for the second part of the project, which was a case-control study measuring HCB and other organochlorines (PCBs, DDE) in the follicular fluid and serum, and evaluating the results by reproductive outcomes in the women concerned. The study gave data on tissue exposure observed in a study group of women who have had in vitro fertilization (IVF). The chemical burden in follicular fluid and serum was compared between two groups — those who had had a pregnancy and those who had not - controlling for various environmental factors. In addition, data on the women who became pregnant were analyzed by reproductive outcome. This adds to our knowledge and is discussed in the second part of this report.

Literature Review

Methods and Materials

Selection of Chemical

The original intent of the study was to conduct a comprehensive literature review on the adverse reproductive effects of the chemicals identified in the serum and follicular fluid in another study (Jarrell et al. 1993b). The chemicals identified in that study include PCBs; HCB; DDE, an ethylene derivative of dichlorodiphenyltrichloroethane (DDT); alphachlordane; and heptachlor epoxide/oxychlordane. The literature selected for review involved studies of humans and animals, both male and female, on the adverse reproductive effects induced by these chemicals. In addition, literature on environmental prevalence and exposure was to be collected. The comprehensive literature search was to include articles from worldwide sources, such as Japan, the Commonwealth of Independent States (the former Soviet Union), Germany, Austria, and Australia.

A broad search through numerous data bases (e.g., MEDLINE, TOXLINE, BIOABSTRACTS, HSDB [Hazardous Substances Data Base]) resulted in an extremely large volume of data. It was estimated that a thorough search would identify 8 000 to 10 000 articles for review. Therefore, it was decided to select only HCB for an extensive review for the following reasons:

- 1. The most common chemicals present in the follicular fluid and serum in the study referred to above by Jarrell et al. (1993b) were HCB and PCBs.
- 2. Only certain PCB isomers have been hypothesized as having toxic reproductive effects; therefore, a literature review on PCBs as a whole was not practical at this stage.
- 3. The inherent toxicity and potential low-level toxicity of HCB are of reproductive concern.
- 4. HCB is listed on the Canadian Environmental Protection Act's Priority Substances List, Group I.
- 5. HCB is one of the top 30 environmental chemicals of reproductive health concern in the report on the regulation of reproductive hazards (Chelimsky 1991).
- 6. HCB is highly persistent in the environment and it has a high potential for bioaccumulation in biologic tissue. In addition, it has been identified worldwide in all compartments of the ecosystem, including air, water, soil, sediment, humans, animals, and foodstuffs. It is one of the major marine water pollutants.
- 7. Even though HCB has been banned from use as a fungicide in North America, it continues to be an industrial waste product in

the manufacture of chlorinated solvents and pesticides. HCB is also prevalent as an unwanted by-product in other industrial processes such as tire manufacturing. Some commercial HCB products contain octachlorodibenzofuran and octachlorodibenzop-dioxin.

8. The review was also undertaken to support ongoing reproductive toxicologic studies on the adverse reproductive effects of HCB.

Design of Search Template

A search template was constructed so that HCB was thoroughly and consistently searched from year to year and from data base to data base. To construct the search template, articles on HCB were obtained and reviewed. A list of adverse reproductive health outcomes related to the exposed males, females, and offspring for both humans and animals was devised. This list was reduced by clumping outcomes into Medical Subject Heading (MeSH) categories, which are used in indexing by the U.S. National Library of Medicine. In addition, infrequent and possible adverse reproductive outcomes as a result of HCB exposure were documented by professional consultation and literature review. A final search template was constructed with the above-mentioned inputs (an appendix on this is available from the archives of the Royal Commission on New Reproductive Technologies).

Selection of Data Bases and Information Sources

Twenty commercial data bases were selected to capture literature from world sources (this appendix is also available). The identification of the relevant data bases was achieved by consulting the following sources:

- National Library of Medicine (Bethesda)
- Reproductive Toxicology Medical Center (Columbia Hospital for Women, Washington)
- Center for Disease Control (Atlanta)
- National Institutes of Health (Washington)
- University of Calgary library
- University of Calgary toxicologist
- Canadian Institute for Scientific and Technical Information (Ottawa)

An attempt to capture unpublished or non-peer-reviewed literature was made by requesting in-house literature and studies from several chemical manufacturers in the United States (an appendix on this is available from the Commission archives). In addition, six relevant papers presented at the seventh meeting of the European Society of Human Reproduction and Embryology and the seventh World Congress on IVF and Assisted Procreation were requested.

Design of Coding Apparatus

Complex coding instruments were designed to capture relevant adverse reproductive health outcomes as reported in the literature and to extract pertinent information from each article. The coding sheets and accompanying keys were developed by reviewing a sample of articles on HCB. Adverse reproductive outcomes and target tissue concentrations were the two major focuses of data extraction. As detailed in the appendix, once the coding instruments were developed, they were minimally altered to address novel outcomes and studies as they occurred.

Gathering, Coding, and Tabulation

An extensive computer literature search was conducted, using the carefully designed search template and accessing the 20 data bases, searching from 1950 to 1992. All references were obtained from CD-ROM diskettes or on-line data base services. The references were transferred to a personal computer and into a reference manager software package. A data base on HCB was constructed from the downloaded sources, and duplicate references were removed. Each reference was reviewed, and all false-positive hits from the original searches were removed. A reference list was made from the new HCB data base, and all obtainable references were acquired from various libraries and agencies in Canada and the United States.

Each article was reviewed, included or excluded, and coded as it was retrieved. Excluded were articles in the following categories:

- did not discuss adverse reproductive outcomes directly related to HCB exposure;
- were unobtainable;
- were unobtainable within the specified time frame of the study;
- were written in a language that could not be interpreted by the investigators; and
- did not report any data or information of importance to the study.

Once the articles were coded they were entered into a statistical software package (SPSS) for analysis. Descriptive statistics and meta-analysis were used to analyze and compile the data bases on adverse reproductive outcomes and tissue level concentrations.

Results from Literature Search

The computer literature search of 20 data bases retrieved 2 842 articles. Of these, 1 414 were either duplicates or obvious false-positive hits and were removed. Over 500 journals were reviewed, covering the last 40 years. Approximately 900 relevant references were acquired from various sources; of these, 363 met the inclusion criteria and were subsequently coded and analyzed.

No response was received from the chemical companies that were contacted, nor were there any replies to the requests to authors for manuscripts.

Summary of the Literature

As can be seen in Tables 1 to 7, there are many reports regarding this particular chemical involving males, females, and the products of

conception.

With respect to males, most of the studies have concentrated on the measurement of HCB and other organochlorines in the seminal fluid. This is not unexpected, because of the high lipid content of semen. Although HCB has been shown to cause alterations in sperm function in vitro (Roediger et al. 1987) and testicular degeneration in the testes when administered to dogs in high concentrations, the associated relationships that exist in contaminated semen do not suggest a major effect.

A larger and more varied body of information exists for females. Several studies have shown the predilection for HCB to enter the ovaries of certain fish and birds (Fathepure et al. 1988). Two major primate studies have shown effects on primordial germ cells (Iatropoulos et al. 1976; Jarrell et al. 1993a). These findings are relevant due to the presence of HCB in human ovarian follicles (Yoshihara et al. 1982; Wagner et al. 1990). Also of some concern are the findings relating a specific lesion to the surface epithelium of the ovary to HCB exposure (Sims et al. 1991). In general, these studies indicate a particular sensitivity of the primordial germ cell of the ovary when HCB is administered. Large gaps exist in our knowledge of the adverse health effects of HCB (e.g., we do not know the no-effect level for oocyte damage). In addition, we have no information on the mechanism of action of this particular chemical.

Studies on neonatal survival and placental and lactational transfer in humans and animals indicate that HCB can be transferred during pregnancy and during lactation. The particular sensitivity of the neonate is possibly due to a combination of its low body fat content, a lack of maternal fat to store the HCB, and the additional increase in HCB due to significant transfer in the milk. HCB does not appear to cause significant congenital malformation. It can predispose to pregnancy loss and stillbirth. It has been classified as a developmental toxicant because of poor postnatal survival. Notably, in animal studies, treatment of the male is not associated with dominant lethals, and the lactational transfer is assumed to be the most vulnerable period.

There were no marked effects on fertility, although reproduction of some submammalian species was inhibited (Persoone and Uyttersprot 1975). There were no increases in cancer and malformation among

humans controlled for the levels of HCB.

Biochemical studies have been extremely varied. Those associated with particular adverse effects have suggested alterations in behaviour (Goldey and Taylor 1991), increased serum levels associated with fasting (Phillips et al. 1989), and the induction of porphyria (Grant et al. 1975a), although it should be noted that oocyte destruction can occur without porphyria.

Table 1. Adverse Reproductive Health Effects of Hexachlorobenzene — Ma

Reference	Outcome	Year	Species	Study type or exposure	Dose
Stachel et al. 1989	Semen density	1989	Human	Correlation	n.a.
Ensslen et al. 1990	Infertility	1990	Human	n.a.	n.a.
Waliszewski and Szymczynski 1983	Binding in semen	1983	Human	n.a.	n.a.
Wagner et al. 1990	Semen concentration				
Szymczynski and Waliszewski 1982a	Varicocele	1982	Human	n.a.	n.a.
Roediger et al. 1987	Semen function	1987	Human	In vitro	0-1 000 hexachl benzol
Szymczynski and Waliszewski 1981	Semen organochlorine	1981	Human	Cross- sectional	

In summary, HCB is present as a persistent chemical in the environment. It is clear that in high concentrations it causes disease and perinatal loss. The effects of the usual levels of exposure are unknown, as the safety factor is not established. The actual impact of HCB on human ovaries is difficult to interpret but raises serious concern.

ue	HCB concentration of tissue (if applicable)	Probability	Total no.	Comments	
en	1.23 ng/mL	n.a.	89	There were no correlations of sperm density with organochloring found in the semen.	
ien		n.s.	156	HCB concentrations do not differentiate those with normal semen function, idiopathic infertility, or pathologic semen parameters.	
nen	68% recovery	n.s.	44	HCB is bound to agents in semen, which gives reduced recoveries for this chemical.	
nen	1.9 ppb	n.a.	79		
icular	n.r.		14	Increased levels of pesticide from left testes in men having bilateral biopsies for varicocele (HCB, DDE, and PCBs). All cases showed teratozoospermia.	
	n.a.	<0.1	n.a.	Dose- and time-dependent effect on sperm motility, forward progression. HOS, vitality, and acrosome reactions. At 1 ng/mL, the adverse effects were significant for HOS.	
nen	34% positive 0.001 μg/g semen	n.a.	50	Note detection limit to maximum level was 0.001-0.010 µg/g. Included seminal plasma and spermatozoa in analysis.	

Table 1. (cont'd)

	Reference	Outcome	Year	Species	Study type or exposure	Dose		
	Szymczynski and Waliszewski 1982b	Semen organochlorine	1982	Human	In vivo	0.001- 0. μg/g		
	Elissalde and Clark 1979	Testosterone metabolism	1979	Mouse	<i>In vivo</i> 21 days	0-250 mg		
	Dougherty et al. 1981	Sperm density	1979	Human	Correlational	n.a.		
	Gralla et al. 1977	Testicular degeneration	1972	Dog	Adult 12 months	1, 10, 10 1 000 m day oral per dog		
	Mann et al. 1988	Sperm contamination	1988	Octopus	In vitro	0, 0.04, 2.4 mg/k		
	n.a. — not applicable n.s. — not significant n.r. — not reported HOS — hypoosmotic swelling							

e	HCB concentration of tissue (if applicable)	Probability	Total no.	Comments
n from m es				New techniques for measuring organochlorine.
	n.a.	<0.05	150	HCB induces a significant enzyme metabolism of testosterone in liver microsome associated with a reduced prostatic and seminal vesicle weight — due to enzyme induction of steroidogenesis in liver.
en	n.a.	<0.05	132	Overall, the multiple correlation coefficient was 0.52; the measured variables of organochlorines accounted for 27% of variances in sperm density. All chemicals had a negative slope. HCB effect was significant (p = 0.036).
	n.a.	n.a.	60	Testicular degeneration in two dogs at the highest dose — associated with weight loss.
n rope	0, 0.04, 0.43, 0.39 ppb	n.a.		Sperm contamination by seawater introduced to spermatophase of giant octopus.

Table 2. Adverse Reproductive Health Effects of Hexachlorobenzene — Female Gonadal

Study type or

Reference	Outcome	Year	Species	exposure	Dose a
Sims et al. 1991	Ovarian histology surface epithelium		Monkey	Adult preconception	0.1, 1.0, 10.0 mg/k 10.0 mg/k BW per d for 90 day
Singh et al. 1990a	Ovarian structure	1990	Monkey	Adult preconception	1.0 mg/kg BW per d for 90 day
Wagner et al. 1990	Follicular fluid concentration	1990	Human	Correlational	n.a.
	Cervical mucus concentration				
latropoulos et al. 1976	Reduction of primary follicles	1976	Monkey	<i>In vivo</i> adult for 60 days	8, 32, 64, 128 mg/k
Knauf and Hobson 1979	Weight loss Ovarian toxicity	1979	Monkey	Adult female	0 mg/k 8 mg/k
					32 mg/k 64 mg/k 128 mg/k 128 mg/k
Sims et al. 1991	Altered surface epithelium	1991	Monkey	<i>In vivo</i> during super- ovulation	0, 0.1, 1.6 10.0 mg/l for 90 day

ше	HCB concentration of tissue (if applicable)	Probability	Total no.	Comments
m			16	HCB induces alterations in the shape of cuboidal epithelium of the ovary at lowest dose (0.1 mg/kg per day).
m			16	HCB induces ultrastructural changes in granulosa theca, and ova consistent with degeneration.
cular	4.32 ppb	n.a.	79	Variations are noted among patients with different clinical diagnoses.
ical us	13.5 ppb	n.a.	79	Levels are high in cervical mucus — similar to breast milk, although there is no fat present.
	n.d.	n.a.	16	Dose-dependent degeneration of primordial germ cells, follicles, and stroma. All endometria were in the follicular phase.
ry 1	Serum ppm <0.1 3.3 0.5 11 1.5 2.5		6	In addition to changes in ovarian and serum HCB levels, there was an associated reduction in cholesterol. These results are a comparison paper showing reduced ovarian follicular numbers at high concentrations.
ım	0.01, 0.16, 0.37 1.31 ppm	7, <0.001	16	Dose-dependent alteration of the surface epithelium of the monkey ovary, with changes in cell shape and degeneration at high concentrations.

Table 2. (cont'd)

D (Outcomo	Year	Species	Study type or exposure	Dose
Reference Jarrell et al. 1993b	Geographic distribution differences	1992	Human	Correlational	n.a.
Muller et al. 1978	Hormonal disruption Anovulation	1978	Monkey	Adult during menstrual cycle	Before and after 4 mg per day
Baukloh et al. 1985	Follicular fluid pesticide	1985	Human	In vivo	n.a.
Sims et al. 1991	Ovarian surface epithelium (% abnormal cells)	1991	Monkey	<i>In vivo</i> 90 days	0, 0.1, 1.0 10.0 mg/k
Singh et al. 1990a	Degenerating ova Degenerating granulosa cells Degenerating theca cells Fibrous ovarian stroma	1990	Monkey	In vitro	0.0, 1.0 mg/kg
Foster et al. 1992	Disrupted ovarian steroidogenesis P ₄ suppression during luteal phase	1992	Monkey	In vivo	0.0, 0.1, 1 10.0 mg/k

1e	HCB concentration of tissue (if applicable)	Probability	Total no.	Comments
ular	0.06 ppb	<0.05	74	There is a significant variation in follicular fluid HCB levels; Vancouver is higher than Hamilton and Halifax.
	n.a.	n.a.	4	Ovulation blocked in 3-4 monkeys with Clophen A30 and 1-4 monkeys with HCB. There were changes in LH or FSH, but low estrogen levels were found in anovulatory cycles. There was an increase in progesterone release after <i>in vivo</i> PCB or HCB exposure.
ular	3.2 ng/mL 1.8 ng/mL	n.s.	12	Follicular fluid concentrations are not correlated with serum. The levels differ (p < 0.05). The burden of follicular fluid content includes PCBs, DDE, and HCB. There is marked variation between sides of the ovary in one subject.
m		<0.05	16	HCB increases the number of abnormal cells on surface epithelium of ovary.
у	n.a.	<0.01	8	HCB exhibited follicle and stromal lesions. Architectural alterations similar to results when dose was at 0.1 mg/kg (see Singh et al. 1990b).
m	n.a.	<0.05	16	Suppression of serum P ₄ concentrations during luteal phase. Broader range of menstrual cycle length and duration of menses with higher dose. Serum E ₂ concentrations were unaffected.

Table 2. (cont'd)

Reference	Outcome	Year	Species	Study type or exposure	Dose
Jarrell et al. 1993a	Destruction of ovarian germ cells	1992	Monkey	In vivo	0.1, 1.0, 10.0 mg/kg
Singh et al. 1990b	Degenerative changes	1990	Monkey	In vivo	0.0, 0.1 mg/kg
Jarrell et al. 1993a	Altered ovarian follicle	1991	Monkey	In vivo	0, 8, 32 mg/kg
n.a. — not applicab n.d. — not determir n.s. — not significa	ned			ot reported ody weight	

Table 3. Adverse Reproductive Health Effects of Hexachlorobenzene — Neonatal Survival (Placental and Lactational Transfer)

Reference	Outcome	Year	Species	Study type or exposure	Dose
Courtney and Andrews 1981	Neonatal tissue concentration	1981	Mouse	Sacrificed on 1 or 20 days post-partum Treated last 4 or 7 days of pregnancy	10, 50 mg

sue	HCB concentration of tissue (if applicable)	Probability	Total no.	Comments
rum ary				Toxic effect in primordial germ cells at lowest dose. No systemic or hepatic effects. No changes in urinary porphyrin excretion.
ary	n.a.	n.r.	6	Degenerative changes in developing ovum, follicular cells, theca follicles. Unaltered surface epithelium.
ary	n.a.	n.r.	4	Increased number of days between menstrual cycle when administered HCB. Reduction in ovarian weight. Loss of normal architecture of the oocyte.
	teinizing hormone Illicle-stimulating ho	rmone	,	ogesterone tradiol

n.r. n.r. Neonatal tissue conce	
and 20. The number does not affect this ris	ween days 1 in the litter

Table 3. (cont'd)

Reference	Outcome	Year	Species	Study type or exposure	Dose
Vos et al. 1971	Tremors Mortality Reproduction reduced Reduced egg volume Reduced hatchability of eggs	1971	Quail	<i>In vivo</i> 90 days adult	1, 5, 20, 80 ppm
Villeneuve et al. 1974	Placental transfer to fetus	1974	Rabbit	Adult pregnancy days 1-27	0, 0.1, 1.0, 10.0 mg/kg
	Fetal death Deformation Resorption Absorption		Rabbit	In vivo 1-27 days pregnancy	1, 1.0, 10 mg/kg
Courtney and Andrews 1979	Tissue concentrations	1979	Mouse	Before implantation sacrificed on day 12 or 17	0, 10, 50, 100 mg/kg per day
	Maternal tissues and fetal placenta			After implantation sacrificed on day 12 or 17	н
Schwetz et al. 1974	Decreased neonatal survival	1974	Quail	<i>In vivo</i> 90 days	20 ppm
Nebecker et al. 1989	Mortality Reproduction Growth	1989	Daphnia Hyalella Gammarus Lumbri- culus Pimephales		Doses up saturation (5 μg/L)

ue	HCB concentration of tissue (if applicable)	Probability	Total no.	Comments
	n.r.	n.r.	74	80 ppm was toxic. Excretion of HCB through the egg reduced brain content in females. HCB reduces reproductive egg volumes and egg hatchability.
		n.a.		Transfer of HCB occurs from mother to fetus (fat > liver > plasma).
	n.a.	n.s.	16	No effects noted on reproduction — HCB is concentrated in the fetal liver.
	n.a.		45	(1) HCB can be mobilized into fatty tissue during pregnancy when animals are treated before implantation.
	n.a.			(2) Mobilization of HCB from mothers to placenta to fetus is rapidly accomplished.
	n.a.	<0.05	32	Decreased chick survival.
	223 μg/g	n.s.	n.a.	HCB has no effect on these crustaceans, worms, and minnows in a chronic flow-through system.

Table 3. (cont'd)

Reference	Outcome	Year	Species	Study type or exposure	Dose
Courtney et al. 1979	Fetal exposure absorption	1979	Rat/ mouse	Mid-gestation 7 days Late-gestation 5 days	0, 10, 50, 100 mg/kg per day
Cripps 1990	Neonatal exposure levels	1990	Rat	Adult during pregnancy	400- 2 000 ppm
Courtney and Andrews 1979	Fetal exposure	1979	Mouse	During pregnancy	10, 50, 100 mg/da
Kitchin et al. 1982	Mortality Fertility Litter size	1982	Rat	Adults mated, delivered, and mated again 96 days pre- mating	60, 80, 100, 120, 140 ppm orally
Gralla et al. 1977	Mortality Anorexia, weight loss, testicular degeneration	1977	Dog	Adult for 12 months in vivo	1, 10, 100, 1 000 mg/ dog
Gocmen et al. 1989	Fetal death Neonatal death	1977- 1987	Human	Mother exposed 40 years ago	
Smith et al. 1987	Goitre, wasting, mortality	1987	Hamster	Adult male	100 ppm (28 weeks 200 ppm (18 + 28 weeks)

500 ppm (6 weeks)

sue	HCB concentration of tissue (if applicable)	Probability	Total no.	Comments
tus corption	n.a.	<0.05	18	HCB resulted in: (1) lower concentrations of HCB in fetus than in placenta, (2) higher HCB concentrations in resorptions, (3) higher gestational concentration of HCB late in pregnancy.
onatal er	27.3 ppm		n.r.	A significant increase in neonatal liver HCB occurs because of transfer from breast milk and low levels of fat in newborns.
iternal od, centa, us	. n.a.	<0.01	46	The fetus is exposed to maternal- stored HCB during pregnancy. Mother > placenta > fetus.
i.	n.a.	n.s.	n.s.	Mortality occurred post-partum afte lactation day 4. No effects on fertility or litter size.
			252	8.3% fetal death, 19.6% neonatal deaths (among the 276 pregnancies of exposed cases). No congenital anomalies. Children did not have elevated porphyrins. Clinically normal exam of survivors.
ì.	n.a.	<0.01	22	All developed goitre; normal T ₄ , low T ₃ . 50% mortality associated with loss of adipose tissues. The changes may reflect chronic disease state on thyroid metabolism.

Table 3. (cont'd)

Reference	Outcome	Year	Species	Study type or exposure	Dose
	Organ weights		•		
Grant et al. 1975c	Hepatic porphyria	1975	Rat	Castrated	100, 500 ppm
Cripps et al. 1984	Human milk contamination Fetal deaths	1984	Human	Poisoning Turkey 1955-61	n.r.
Gilbertson and Fox 1977	Embryo morbidity, reduced hatching	1977	Herring gulls	Herring gulls collected in 1974	n.a.
Kavlock et al. 1987	Teratology development	1987	Mouse	In vivo 8-10 days' gestation	125 mg/kg PO (oral gavage)
Cripps 1981	Reproduction	1981	Human	In vivo poisoning 1956-58	Milk s.d. 0.27 ppm ± 0.423 SD Fat s.d. 0.22 ppm ± 0.14 SD
Hansen et al. 1985	Hatching	1985	Fish Baltic herring	Analytical	<1-8.6 <1-4.5 <1.39 mg/k
Dunn et al. 1979	Death Hatchability	1979	Hens	27 weeks in feed containing PCNB contaminated with HCB	n.r.

Table 3. (cont'd)

				Study type or	
Reference	Outcome	Year	Species	exposure	Dose
Calamari et al. 1983	Growth inhibition	1983	Aquatic organisms	n.r.	n.r.
Krishnan et al. 1991	Hepatic porphyria	1991	Rat	6 weeks 3 weeks	10 mg/kg 100 mg/kg
Kavlock et al. 1987	Decreased pregnancy rate Increased resorption Increased neonatal death	1987	Mouse	In vivo	0.125 mg/k
Courtney and Andrews 1985	Lactational transfer	1985	Mouse	In vivo	0, 1.0, 10.0 50.0 mg/kg
Bailey et al. 1980	Lactational transfer	1979	Monkey	In vivo	64 mg/kg
Bleavins et al. 1982	Decreased birthweight Increased kit mortality Decreased fertility	1982	Ferret Mink	In vivo	0, 1, 5, 25, 125 ppm
n.r. — not rep n.a. — not ap			n.s. s.d.	not significan significantly of	

ue	HCB concentration of tissue (if applicable)	Probability	Total no.	Comments
	n.a.	n.d.	n.r.	HCB reduces growth of algae and fertility tests of <i>Daphnia sigma</i> .
	ń.a.	<0.05	n.r.	Porphyria in rat is associated with administration of threshold dose of HCB. There is a delay in excretion of porphyrins until this dose is reached.
	n.a.	<0.05	70	Decreased pregnancy rate of 43% compared with control, 7% increase in resorption, 27% neonatal deaths.
r n cle	n.a.	<0.05	140	Body burden in neonates exposed by lactational transfer was higher than that in the neonates exposed only by gestational transfer. Lactational transfer is major route of excretion (95% HCB was depleted during 20 days of lactation).
od e row ∋nals	n.a.	n.r.	4	Tissue levels of HCB were higher in infants than in mothers when their only source of HCB was lactational transfer. HCB concentrated in infant fat, bone marrow, adrenals, ovaries, lymph nodes, and liver. Suggests that nursing infants are at higher risk than their mothers.
	n.a.	n.r.	n.r.	Birthweights were reduced and weight gains were reduced. Dose relation to kit mortality. No offspring produced at 125 ppm.
	standard devia not determined		PCNB PO	pentachloronitrobenzene per os (by mouth)

Table 4. Adverse Reproductive Health Effects of Hexachlorobenzene — Fertility

Reference	Outcome	Year	Species	Study type or exposure	Dose
Mendoza et al. 1979	Hepatic porphyrin Resorption Mating	1979	Rat	Two weeks before mating until end of experiment	80 ppm
Simon et al. 1978	Dominant lethal effect	1978	Rat male	Adult males 5 days prior to mating	0, 70, 221 mg/kg per day for 5 days
Silkworth et al. 1986	Decrease net weight gain Skeletal anomalies Resorption Stillbirth	1986	Rat	Pregnancy days 6-15	0, 25, 75, 150, and 250 mg/kg per day
Nebecker et al. 1989	Growth Reproduction	1989	Inverte- brates and fish	2-68 days flow-through	233 μg/g
Khera 1974	Anomalies Pregnancy loss	1974	Rat female	In vivo toxicity during pregnancy	0-120 mg/k
Leoni et al. 1989	Miscarriage	1989	Human	Case-control	n.a.
Persoone and Uyttersprot 1975	Rate of reproduction	1975	Marine ciliate	In vitro	0.01, 0.1, 1 10 ppm

fissue	HCB concentration of tissue (if applicable)	Probability	Total no.	Comments
1.a.	n.a.	n.s.	20	HCB does not affect main outcomes of adult rats treated prior to pregnancy experiment at concentrations that increase hepatic porphyrins.
1.a.	n.a.	n.s.	30	HCB in the adult male is not associated with dominant lethal effects in female rats.
1.a.	n.a.	<0.05	68	These outcomes have a dose- related effect. Love Canal soil
		<0.05		extract has approximately 0.05% HCB.
		<0.05 <0.05		nob.
i.a.	n.a.	n.s.	n.r.	No effect of HCB on growth or reproduction.
; ₁.a.	n.a.		240	HCB induced a significant increase in reduced fetal weight at high doses. There was a significant increase in 14th rib as a function of dose, duration, and maternal toxicity. No effect on embryo loss during pregnancy.
ICB blood: ase 1.60 pb, control :49 ppb	n.s.	n.a.	120	PCB effect was most substantial. Blood samples differed among 110 women with miscarriages with respect to PCBs (p < 0.05) (cases = 8.65 ppb; control = 6.89 ppb; t = 1.68) but not HCB or DDE.
sa.	n.a.	n.a.		HCB inhibits growth in Euplotes vannus.

Table 4. (cont'd)

Reference	Outcome	Year	Species	exposure	Dose
Parasher et al. 1978	Growth	1978	Algae	In vitro 76 hours in acetone	110 ppm
Kavlock et al. 1987	Decreased pregnancy rate Increased resorption Increased neonatal death	1987	Mouse	In vivo	0.125 mg/kç
Von Westernhagen et al. 1987	Loss of reproductive capacity	1987	Fish	In vivo	n.a.

Study type or

n.a. — not applicable n.s. — not significant n.r. — not reported

Table 5. Adverse Reproductive Health Effects of Hexachlorobenzene — Egg Production

Reference	Outcome	Year	Species	Study type or exposure	Dose
Smith and Cabral 1980	Liver cell tumours	1980	Rats	<i>In vivo</i> in diet 70-90 weeks	100 ppm
Sakamoto et al. 1981	Egg production	1981	Quail	Adult 56 days treatment 30 days depletion	0, 50, 50 ppb

n.a. — not applicable

n.r. — not reported

n.s. — not significant

Table 6. Cancer or Malformation Possibly Resulting from Exposure to Hexachlorobenzene

Reference	Outcome	Year	Species	Study type or exposure	Dose
Teufel et al. 1990	Cancer Malformations	1975	Human	183 controls 33 malfor- mations 46 cancers	
Andrews and Courtney 1986	Enlarged kidney	1986	Mice	In vivo	0, 1.0, 10.0 mg/kg
	Hydronephrosis				

n.a. — not applicable

n.s. — not significant

ssue	HCB concentration of tissue (if applicable)	Probability	Total no.	Comments
à.	n.a.	n.s.	262	No elevation in adipose HCB concentrations among the groups.
rer dney	n.a.	<0.05	28	Mice exposed <i>in utero</i> days 6-16 of gestation displayed enlarged kidneys and hydronephrosis.
				Significant increase in kidney/body weight ratio and liver/body weight ratio.

Table 7. Biochemical Effects of Hexachlorobenzene

Reference	Outcome	Year	Species	Study type or exposure	Dose
Goldey and Taylor 1991	Behavioural toxicity	1991	Rat	Adult	0, 10, 100 mg/kg per day
Arnold and . Krewski 1988	Adenomatous hyperplasia Liver tumours Pituitary tumours	1988	Rat	Adult	0, 0.32, 1.6 ppm
Villeneuve 1975	Appetite loss Tremors Death Redistribution or mobilization outcome	1975	Rat	Food restriction to 25% after dosing as adult for 14 days	0, 1, 10, 100 mg/kg
Gomez-Catalan et al. 1991	Plasma concentrate	1991	Rat	n.a.	n.a.
			Human		
Phillips et al. 1989	Serum levels	1989	Human	Cross-sectional adult	
Sweeney and Jones 1976	Sex differences and porphyria	1976	Rat	In vivo	0.25% in di

ssue	HCB concentration of tissue (if applicable)	Probability	Total no.	Comments
1.	n.a.	n.r.	n.r.	HCB is a behavioural teratogen. Comments expressed on need to study entire litter over long periods of time post-treatment.
		<0.05	146	Dose-response effects present using exact rather than approximate test for linear dose
		<0.05		response.
		<0.05		
lain	>300 ppm	<0.05	60	Food restriction causes a mobilization of HCB stored in fat, which causes it to enter plasma and brain.
f.t blood: psma ols	13.0% 87.0%		4	There is a higher proportion of HCE in the plasma of blood in humans than in rats.
man lod: Isma (Is	69.8% 30.2%		4	
fnale	0.170 mg/g serum 0.127 mg/g serum 0.0243 µg/g lipid 0.0212 µg/g lipid		20	Fasting and feeding have an effect on serum concentrations. Considerations of lipid levels may remove sex differences in concentrates. Compare serum values on a μg/g lipid basis.
in Di				Increased susceptibility of female rats to porphyria associated with decreased drug metabolizing enzyme (DME) induction compared with males. Intact testes confer some protection.

Table 7. (cont'd)

Reference	Outcome	Year	Species	Study type or exposure	Dose
Graef et al. 1982	Steroidogenesis	1982	Rat	<i>In vivo</i> 55 days	0.05% in d
Rozman et al. 1978	Biochemical parameters: Serum estrogen Progesterone FSH LH SGOT SGPT LDH Cytochrome P-450	1978	Monkey	In vivo 18 months	1 ppm
Richter et al. 1981	Sex differences in biotransformation	1981	Rat	In vivo assessed 3-52 days after last dose	
Peters et al. 1989	Central nervous system extra- pyramidal symptoms	1989	Human	Cross-sectional	n.a.

ssue	HCB concentration of tissue (if applicable)	Probability	Total no.	Comments
а.	n.a.	n.r.	24	HCB induces porphyria in rats and decreases hepatic NADPH 5α -reduction of HCB. Suggests that 5β -steroids are increased due to HCB and are associated with increased porphyria. Regulation of NAD/NADPH $5\alpha/5\beta$ reductase may be relevant to development of porphyria.
ood male 50 days)	0.22 ppm	n.s.	6	No sex difference in serum levels or weight gain of animals. No evidence of harmful effect.
ood nale 50 days)	0.27 ppm			CVICTOR OF THE THE COOK
stis	0.3 ppm	n.s.		
rer ale male CTP) at days	0.116, 0.373 mg/kg	<0.05		Higher concentration of PCTP in females than in males. HCB decreased slower in serum in females.
	n.r	n.d.	267	There has been an evolving pattern of extra-pyramidal symptoms since 1977 among survivors of HCB poisoning in Turkey.

Table 7. (cont'd)

Reference	Outcome	Year	Species	Study type or exposure	Dose
Mull et al. 1978	Growth rate Alk. phos. act. GOT G-6-PDH	1978	Ewe (castrated)	a) 90 days followed for 210 days after dosing	
	SDH Plasma protein HCT			b) acute exposure 14 days	100 ppm
	Metabolism of antipyrine, microsomal N-demethylase, microsomal D-demethylase				
Burns and Miller 1975	Sex difference in concentration	1975	Human	Case-control	n.a.
	Proximity to exposure and contraction				
	Cutaneous porphyria				n.a.
Grant et al. 1975a	Porphyria	1975	Rat	Adult 21-104 days	0, 0.5, 2, 8 32 mg/kg
				7-231 days	0, 0.5, 2, 8 32 mg/kg
Mollenhauer et al. 1976	Ultrastructure change in liver	1975	Rat	3-12 months	1-25 ppm

ssue	HCB concentration of tissue (if applicable)	Probability	Total no.	Comments
	n.a.	n.s.	50	Growth rate of the animals was normal.
		n.s.		There were no changes in the hepatic architecture histologically. These enzymes were increased in
		<0.05		either the 90-day or the 14-day acute exposure. This was associated with increased microsomal protein concentrations.
		<0.01		miorosomai protoin concentrations.
		<0.01		
rum	Case 2.4 ppb Control 0.5 ppb	<0.001	86	Exposed individuals have higher concentrations.
	Female 2.79 ppb Male 4.71 ppb	<0.05		Females are lower than males, serum LDH higher in cases.
n	n.a.	n.s.		Not present in exposed cases.
		<0.05	200	Female rats are more sensitive in developing porphyria. Porphyrins persist after discontinuing HCB for
		<0.05		231 days. HCB induces porphyria and induces microsomal drug metabolizing system, including P-450. Females are more susceptible than males.
	n.a.			Degenerative lipid droplets found to be autodigested. Suggests that autodigestion represents a way of eliminating HCB from liver. Some enlarged mitochondria are also present.

Table 7. (cont'd)

	Outroms	Year	Species	Study type or exposure	Dose
Mendoza and Watanabe 1978	Biliary estrogen excretion	1978	Rat	Adult 5 or 8 weeks	80 ppm
Geike and Parasher 1976a	Growth	1976	Algae	10 days in vitro	0-0.05 ppm
Mendoza et al. 1977	E ₂ Progesterone LH FSH	1977	Rat		
Pant et al. 1982	Nerve toxicity Acetylcholines- terase inhibition in insects	1982	Philosamia ricini larvae	In vivo toxicity acute dosing	75 μg HCB/larva
Braune and Norstrom 1989	Biomagnification in tissues	1989	Herring gul	l Correlational	n.a.
Gilbertson and Fox 1983	Chick edema, disease, hepatic porphyria	1983	Gull embryos	Correlational	

sue	HCB concentration of tissue (if applicable)	Probability	Total no.	Comments
er: reeks reeks rus:	47.5 ppm 71.8 ppm	<0.01	10	HCB induces an increase in the excretion rate of estrogen due to the stimulation of increased glucuronidation associated with
eeks eeks :	91.6 ppm 13.6 ppm			increased porphyrin production. These occurred after feeding for 8 weeks.
eeks eeks	1.01 ppm 2.55 ppm			o woods.
ae	n.a.	n.d.	n.r.	HCB caused dose-related decrease in algae growth associated with an increase in porphyrins and a decrease in nitrogen and carbohydrates. Possible nutritional mechanism for reduced growth rates.
		<0.01 for PC	В	Authors also report that ovariectomized rats given Gn-RH while treated with HCB or PCBs did not have a change in serum LH or FSH, indicating no alteration of pituitary function. Therefore (1) low estrogen involved in blocking ovulation; (2) low estrogen may be at ovary or liver.
	n.s.	n.a.	n.s.	HCB acts as a neurotoxin to P. ricini larvae by inhibiting acetylcholinesterase activity and releasing all nutrients.
er I	0.05 mg/kg 0.1 mg/kg wet weight	n.a.	10	HCB has relatively high biomagnification factor and is concentrated in the egg more than in the liver.
er j	2.79 ppm (cases) 0.22 ppm (control)	<0.05	n.a.	Geographic relationship to reproductive outcomes.

Table 7. (cont'd)

Reference	Outcome	Year	Species	Study type or exposure	Dose at
Rozman et al. 1977	Enzyme induction	1977	Monkey	<i>In vivo</i> chronic 15 months	¹⁴ C-labelle HCB 110 μg/da
Sadana and Henley 1985	Brain enzyme activation	1985	Rat	60 days	1 g/kg
Andrews et al. 1989	Hyperpara- thyroidism	1989	Rat	5 days/week for 5, 10, 15 weeks	0.1, 1.0, 10.0, 25.0 mg/k
Kimbrough and Linder 1974	Adrenal hyperplasia	1974	Rat	4 months dosing orally	0, 100, 1 000, 1 500 ppn
Hansen et al. 1979	Adrenal hyperplasia	1979	Hens	25, 38, or 52 days	0, 1, 10, . 100 ppm
Hansen et al. 1977	General health	1977	Pig	13 weeks	0, 1, 10, 100 ppm
Sundlof et al. 1981	Weight loss Abnormal electro- encephalogram	1980	Dog	In vivo	50.0, 150.0 mg/

sue	HCB concentration of tissue (if applicable)	Probability	Total no.	Comments
nary tabolites	n.a.	n.a.	6	Marked increase in the number of urinary metabolites of HCB, indicating possible enzyme induction in response to treatment.
	n.a.	<0.05	n.r.	Different areas of the brain demonstrated different activation/ deactivation enzymes as a consequence of HCB administration.
%	n.a.	<0.05	160	HCB-induced hyperparathyroidism as shown by increased serum PTH levels and osteosclerosis of femur.
•	n.a.	<0.05	120	Adrenal hyperplasia present at 500 ppm.
	n.a.	<0.05	50	Significantly enlarged adrenal. Slow elevation to equilibration with adipose HCB.
			20	Doses did not produce ill health. HCB collected in adipose tissues. High dose had a tendency for smaller spleens and larger livers.
		<0.05	13	Unpredictable effect of HCB on haematology. Severe hepatic damage not indicated. Abnormal encephalogram pattern, suggesting physiologic change.

Table 7. ((cont'd)
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Reference	Outcome	Year	Species	Study type or exposure	Dose
Villeneuve et al. 1977	Induction of microsomal enzyme activity Higher tissue accumulation due to food deprivation	1976	Rat	In vivo	0, 20, 40, 100, 200 ppm
n.r. — not n.d. — not n.s. — not FSH — foll LH — lute SGOT — ser SGPT — ser LDH — lac alk. phos. act. — alk	applicable reported determined significant icle-stimulating hore sinizing hormone rum glutamic-oxaloa rum glutamate-pyrur tate dehydrogenase aline phosphatase tamine-oxaloacetic	acetic tran vase trans e activity	saminase		

Follicular Fluid Study

Introduction

Several reports (Szymczynski and Waliszewski 1982a, 1982b; Cripps et al. 1984; Courtney et al. 1985; Stachel et al. 1989; Wagner et al. 1990) have demonstrated that relevant organochlorines can be isolated from reproductive tissues such as semen, follicular fluid, and breast milk. Whether and how these chemicals alter reproductive functions are as yet unknown, although the presence of mutagenic agents in follicular fluid at the time of the resumption of meiosis is reason for concern.

A previous investigation for the Environmental Health Directorate, Health and Welfare Canada (Jarrell et al. 1993b), was undertaken to measure the degree of contamination of ovarian follicles by organochlorines in women from various areas across Canada who had had IVF. The levels were analyzed by several factors, including age, city location, source of

ue	HCB concentration of tissue (if applicable)	Probability	Total no.	Comments
ma r n enal		<0.05	36	Food deprivation resulted in higher plasma, liver, brain, and adrenal accumulation. HCB in both males and females. Also augmented induction of microsomal enzyme activity.
PDH I PPH	— pentachloro	hydrogenase e adenine dinu e adenine dinu othiophenol	ucleotide ucleotide pho	sphate (reduced)
?H ?:	 gonadotrop parathyroid ¹⁴C-labelled Head	hormone		urity > 99.9%.

drinking water, fish consumption, and weight loss. The most significant finding was that the location (i.e., Halifax, Vancouver, or Hamilton) predicted the levels of HCB and PCBs in both the serum and the follicular fluid. Reproductive effects were evaluated by the outcome of the IVF cycle at the time of sample collection and by the embryo growth in culture prior to embryo transfer. The prior reproductive history of these patients was not recorded.

The focus of the current study was to evaluate whether the chemical concentrations differed by categories of previous reproductive history. Although the entire patient population was infertile, it was hypothesized that the category of previous reproductive history might differ according to the levels of HCB found. The study examined whether this was the case.

Materials and Methods

The patients in this study had previously participated in the IVF programs at the University of British Columbia, Dalhousie University, and

McMaster University. They were asked to complete a questionnaire (Appendix 2), which included variables related to reproductive events, smoking, and illicit drug use. All protocols were approved by the institutional review boards before submission. In some cases, direct communication was used to complete the questionnaires. Of the 76 original patients, 49 (64%) completed the second study.

The serum and follicular fluid analysis data were collected in ASCII format from the Environmental Health Directorate and were subjected to statistical analysis in relation to the environmental questionnaires using SPSS. Since many of the values were below the detection limit (DL), the concentrations were transformed to $\log_{10}{(1 + C)}$, where C was the level of the chemical measured. Values that were undetectable were transformed to $1/2\log_{10}{(1 + DL)}$, which was 0.01 ppb for HCB and PCBs and 0.02 ppb for DDE.

Determination of significant predictive variables was carried out using forward multiple regression. The predictor variables included previous pregnancy, age, residence (urban or rural), source of drinking water, smoking history and history of alcohol consumption, location (Vancouver, Halifax, or Hamilton), height, weight, and fish and sportfish consumption. The analyses were conducted for the dependent variables of serum and

follicular fluid HCB, PCBs, and DDE after log transformation.

Results

Forty-nine patients agreed to participate in this additional study. Sampling was limited compared with that in the initial study; therefore, it is inappropriate to make direct comparisons with the previous study. This study used the same technique of forward multiple regression analysis, but reported only for the effects of including reproductive outcome. Characteristics of the patients are presented in Table 8. Results of untransformed organochlorine levels from serum and follicular fluid are presented in Table 9.

Patients who had had a previous pregnancy were found to have significantly less PCBs in the follicular fluid (p = 0.012) and serum (p = 0.002) (Table 10). There was, however, no such difference noted for HCB in the follicular fluid (p = 0.370) or serum (p = 0.696) or for DDE in the follicular fluid (p = 0.374) or serum (p = 0.798). To observe the possible influence of the different types of pregnancy outcomes, the frequencies of the various reproductive outcomes and respective mean follicular fluid PCB levels are presented in Table 11. Again, the major effects observed were primarily the mean levels of those patients who had never conceived.

To account for the effects of other variables that might influence serum and follicular fluid concentrations, forward multiple regression was used, with HCB, PCBs, and DDE selected as the dependent variables. With respect to follicular fluid PCB concentration, previous pregnancy was found to be highly significant (p = 0.004), whereas other environmental factors

were not selected by the analysis. This same analysis did not demonstrate that any variable was significant in the prediction of serum PCBs or serum or follicular fluid HCB or DDE (Table 12). It should be noted that when previous pregnancy was eliminated from the analysis, location was seen to have greater predictive value in the analysis.

Total no. of subjects	49
Age (years)	31.9 ± 3.4
Height (inches)	63.4 ± 4.2
Weight (pounds)	143.6 ± 28.3
Location Hamilton Halifax Vancouver Not listed	18 21 8 2
Previous pregnancy experience (total cases) Abortion Ectopic pregnancy Live birth	36 16 35 28
Individual patient experience Abortion(s) Ectopic pregnancy(ies) Live birth(s) alone Combinations of live births with abortion(s) and/or ectopic pregnancy(ies)	8 13 9

Table 9. Concentrations of Priority Chemicals in Serum and Ovarian Follicular Fluid

Chemical	Mean	Standard deviation	Min.	Max.
ffPCBs	0.86	2.25	0.00	10.40
sPCBs	1.50	2.83	0.00	13.10
ffHCB	0.10	0.13	0.00	0.21
sHCB	0.23	0.24	0.00	1.10
ffDDE	0.61	0.41	0.00	2.10
sDDE	1.29	1.20	0.00	6.60

Note: Values represent the untransformed concentrations (in ppb) of PCBs, HCB, and DDE in the serum (s) and follicular fluid (ff).

Table 10. Comparison of Transformed Concentrations (in ppb) of PCBs, HCB, and DDE Among Those with a Previous Pregnancy and Those with No Previous Pregnancy

Not pregnant	Pregnant	Probability
0.5024 ± 0.407	0.1539 ± 0.284	0.002
0.3297 ± 0.442	0.0877 ± 0.191	0.012
0.0806 ± 0.042	0.0897 ± 0.073	0.696
0.0583 ± 0.052	0.0460 ± 0.035	0.370
0.2800 ± 0.164	0.3335 ± 0.176	0.798
0.2043 ± 0.073	0.1954 ± 0.106	0.374
	0.3297 ± 0.442 0.0806 ± 0.042 0.0583 ± 0.052 0.2800 ± 0.164	0.3297 ± 0.442 0.0877 ± 0.191 0.0806 ± 0.042 0.0897 ± 0.073 0.0583 ± 0.052 0.0460 ± 0.035 0.2800 ± 0.164 0.3335 ± 0.176

Table 11. Reproductive Outcomes and Follicular Fluid (ff)
Concentrations (in ppb) of Polychlorinated Biphenyls (PCBs)

Reproductive outcome	No.	ffPCBs
Ectopic	14	0.0212
Abortion	9	0.0212
Live birth	9	0.0833
Combination	10	0.2048
Non-pregnant	11	0.3297

Note: Values represent transformed concentrations.

Table 12. Correlation Between Serum and Follicular Fluid Concentrations (in ppb)

HCB	0.3746*
PCBs	0.3159
DDE	0.3433*

^{*} p < 0.01.

Discussion

Inclusion of reproductive outcomes was shown to have a marked effect on follicular fluid PCB concentrations among infertile patients receiving IVF treatment in the initial study. Simple comparisons of concentrations between groups with different reproductive histories showed that women who had not conceived had very high serum and follicular fluid PCB concentrations. These levels were significantly greater than those found among women who had conceived. Despite the similar forward multiple regression techniques used in the two studies, the strength of geographic location as the major predictor was not observed. Instead, previous pregnancy was shown to be a strong predictor of follicular fluid PCB concentrations. These findings indicate that in the assessment of PCB levels at least, prior reproductive performance should be given particular consideration.

It is tempting to speculate that there is a cause-and-effect relationship between high concentrations of organochlorines and infertility. Certainly,

PCBs are associated with a variety of adverse reproductive outcomes, and the possibility of a similar association among women cannot be excluded.

Another, perhaps more plausible, interpretation of the findings is that women who have conceived have also had a significant transfer of PCBs from their tissue compartments to the products of conception — placenta, fetus, and newborn — by the processes of transplacental transfer and breast feeding. The actual contribution of such factors cannot be assessed in this study, as the sample size is limited and the frequency of breast feeding was not obtained.

The significance of these findings lies in applying this question to the large body of tissue and serum measurements of PCBs throughout the world. Although it is consistently noted that the levels tend to be lower in women than in men, there is no correction factor to establish whether or not a woman has had previous pregnancies. An appropriate recommendation from a regulatory standpoint would seem to be that interpreting exposure to PCB data will be more relevant and understandable if such concentrations are categorized on the basis of prior pregnancy experience and breast-feeding history. Furthermore, it would be appropriate to recommend that analyses be carried out to measure the relative contributions of pregnancy, with or without breast feeding, to serum PCB levels.

Summary

This project was carried out to evaluate further the concept that the follicular fluid surrounding the oocyte contains highly toxic chemicals close to the time of ovulation. Because the egg is exposed to these chemicals at a time when the deoxyribonucleic acid may be particularly susceptible to injury, evaluation of factors that affect these concentrations is relevant to human reproduction in the female.

The purpose of the first segment of this study was to evaluate, through a literature review, several chemicals in the follicular fluid to establish the known risks to reproduction. Because of the extensive number of reports available, it was possible to study only HCB. In addition, because there is a concerted effort under way to evaluate specific congeners of PCBs, it was not considered an appropriate time to conduct an extensive literature

search of PCBs in general.

The major adverse effects noted for HCB were related to the reproductive system. Specifically, the gonad seems to be a particular target for uptake. In some avian species, there is a marked uptake of HCB into the ovary and the egg and a measurable transfer of hepatic HCB into the egg. Although concentration of the chemical in the gonads of certain avian species does occur, it is not evident that it occurs in humans. In fact, it would appear from several studies of ovarian follicular fluid that concentration in the follicular fluid is not occurring. Uptake is also a major factor in the male, as shown by the frequent isolation of HCB from the semen. However, what is not apparent is whether the presence of HCB in these gonadal tissues is associated with any evidence of adverse function.

In determining whether adverse effects are occurring at low concentration, the pertinent effect to observe must be established. In the primate ovary, at least two tissues act as targets for HCB. The first is the primordial germ cell, as HCB can induce the virtual absence of ova in rhesus and cynomolgus monkeys. The second target is the surface epithelium of the ovary. These tissues are affected at the lowest concentrations now used (0.1 mg/kg per day); this is still a high total treatment dose but, significantly, the actions on the gonad at this level do not show systemic toxicity.

Another reproductive effect is the transplacental and lactational transfer of HCB to the fetus and neonate, respectively. Such transfer is relevant because it occurs to a susceptible recipient that cannot deal with the concentrations adequately because of relatively low body fat concentrations. This was the cause of the high rate of neonatal mortality identified in Turkey as a result of HCB poisoning during the 1950s. These observations have been substantiated by a large series of animal studies (refer to references listed in Table 3).

Although egg effects occur in a variety of avian species, there is little measurable effect on fertility among mammals treated during pregnancy. This is consistent with the finding that cynomolgus monkeys treated with HCB in high doses will lose ovarian germ cells, yet the menstrual cycles persist and the response to IVF of the ovulated oocytes is not compromised. The lack of a dominant lethal effect is reassuring, particularly since the chemical is present in the semen. It is also reassuring that case-control studies have not shown that HCB is associated with cancer or malformations.

This review indicates that monitoring the ovarian follicle would provide information relevant to human health concerns. However, just what adverse effect can be monitored needs to be determined.

The case-control study of the reproductive performance of women who have had follicular fluid aspiration and pesticide measurements during IVF provides additional perspectives. The initial study was intended to evaluate reproductive performance by analyzing organochlorine concentration and oocyte recovery and embryo development; no effects were identified. This follow-up study was conducted to look at whether women's prior reproductive performance differed based on the levels of the organochlorines. There are many complexities associated with such a study. For example, concentrations at the time of analysis may not reflect concentrations at the time of significant reproductive events such as pregnancy or abortion.

Despite the complexities, an important observation has been made suggesting that the serum and follicular fluid PCB levels in women may differ depending on prior reproductive performance. This was not seen to the same degree for HCB or DDE, which may mean that there is a chemical

specificity to this differentiation. Certainly, the fact that the levels are considerably higher among infertile women with no pregnancies than among infertile women with prior pregnancies suggests that an anti-fertility effect of PCBs cannot be excluded. It is also possible that the prior pregnancy lowered the levels of organochlorines.

On the basis of the review and the analysis of the reproductive histories of the patients with prior follicular fluid analysis, four

recommendations can be made:

- 1. Support the monitoring of human ovarian follicular fluid for priority chemicals to further establish normative data, and collect data on prior reproductive events in these women, through continual review of patients receiving IVF.
- 2. Support the monitoring of serum PCBs with the purpose of evaluating any relation to infertility using appropriate epidemiologic study.
- 3. Support the appropriate use of animal studies to assess the mechanism of action of such ovarian toxicants.
- 4. Support the reporting by regulatory agencies of the concentrations (by categories) of priority organochlorines, along with information on prior reproductive experience and breast-feeding history.

Appendix 1. Adverse Health Outcomes

	Total number of occurrences		
Outcomes	Positive	Negative	
Musculoskeletal			
Arthritis	1	0	
Osteosclerosis	1	0	
Weakness	1	0	
Respiratory			
Cardio/respiratory failure	1	0	
Decreased natural killer activity in lung	1	0	

Table 1A. (cont'd)

	Total number of occurrences		
Outcomes	Positive	Negative	
Nervous system			
Depression	1	0	
Convulsions/seizures	1	0	
Tremors	4	0	
Hyperexcitability/hyperactivity	1	1	
Decreased dopamine (hypothalamus)	1	0	
Neurotoxin (inhibit acetylcholinesterase)	1	0	
Decreased motor response	1	0	
Parkinsonian symptoms	1	0	
Brain enzyme activation	1	0	
Electroencephalograph dysrhythmias	1	0	
Tumour induction		0	
	2	0	
_iver Increased weight of liver	6	0	
Degenerative change in liver (hepatic-ultrastructures)	4	0	
Hepatic porphyria	1		
Tumour induction	1	0	
	'	U	
Kidney			
Degenerative change	2	0	
Increased kidney weight	1	0	
Hydronephrosis	1	0	
Skin			
PCT (porphyria cutanea tarda)	3	0	
Pembe yara (pink sore)	1	0	
Hirsutism	2	0	
Haematology/lymphatic/hormonal			
Serum follicle-stimulating hormone decrease	1	0	
Serum luteinizing hormone decrease	1	0	
Serum estradiol decrease	1	0	
Serum testosterone decrease	1	0	
Serum progesterone decrease	2	0	
Anaemia, NOC	1	0	
Luteinizing-hormone-induced progesterone synthesis	1	0	
Low estrogen levels	1	0	
Endocrine			
Decreased thymus weight	1	0	
Adrenal hyperplasia	2	0	
Hyperparathyroidism	1	0	
Pituitary adenoma	1	0	

Table 1A. (cont'd)

	Total number of occurrences		
Outcomes	Positive	Negative	
Metabolic and nutritional Loss of appetite	1	0	
Urogenital — female		•	
Premature menopause/premature ovarian failure	1	0	
Anovulation	1	0	
Increased ratio of corpora lutea	1	0	
Decreased ovarian weight	1	_	
Deterioration of ovary, NOC	1	0	
Deterioration of ovarian follicles and ova, NOC	3	0	
Altered ovarian surface epithelium/cell destruction	6	0	
Decreased number of follicles	2	0	
Adenomatous hyperplasia	1	0	
Development of prolonged cycles	1	0	
Organelle degeneration	2	0	
Ovarian surface epithelium (% of abnormal cells)	1	0	
Degenerating ova	2	. 0	
Degenerating granulosa	1.1	0	
Degenerating theca cells	2	0	
Disrupted ovarian steroidogenesis	1	0	
Suppressed P ₄ -level (luteal phase)	1	0	
Pregnancy			
Spontaneous abortion/pregnancy loss	3	0	
Stillbirth/neonatal death/fetus not viable	11	0	
Decreased birthweight	4	0	
Resorption of pregnancy	3	0	
Decreased pregnancy rate per cycle	1	0	
Decreased pregnancy rate	1	0	
Placental transfer of chemical	13	. 0	
Lactational transfer of chemical	9	0	
Urogenital — male			
Impaired spermatogenesis, NOC	1	0	
Decreased sperm motility	1	0	
Decreased testes weight	1	0	
Contamination of seminal fluid	1	0	
Decreased sperm density	2	.0	
Testicular degeneration	1	0	
Semen binding of chemicals	1	0	
Hypoosmotic swelling	1	0	
Varicocele (high content of HCB)	1	0	

Table 1A. (cont'd)

	Total number of occurrences		
Outcomes	Positive	Negative	
Second generations			
Clubfoot	1	0	
Cleft lip and palate	1	0	
Rib defects	1	0	
Renal agenesis	1	0	
Increased rate of malformations or			
malformations, NOC	4	0	
Increased rate of childhood cancer			
or childhood cancer, NOC	1	0	
Death (viability)/neonate mortality	6	0	
Skeletal abnormality	1	0	
Liver degeneration	1	0	
Kidney degeneration	1	0	
Miscellaneous effects			
Weight gain	1	0	
Weight loss	1	0	
Biotransformation difference between males			
and females	2	0	
Persistent HCB intoxication effects	1	0	
Chromosome abnormality	1	0	
Decreased rate of implantation/			
inhibition of implantation	1	0	
Outcomes specific to animal studies			
Decreased eggshell thickness	2	1	
Clutch size decrease	1	0	
Decreased egg production	1	0	
Infertile eggs	2	0	
Egg viability (hatchability)	2	0	
Mating index low	1	0	
Decreased growth	6	1	
Contamination of sperm	1	0	
Edema	1	0	
Biomagnification in tissue	1	0	
Enzyme induction	15	0	
Decreased fertility (over generations)	1	0	
Death	1	0	

Table 1A. (cont'd)

	Total number of occurrences	
Outcomes	Positive	Negative
Bioassays/cell change		
Mammalian mutagenesis	2	0
Granulosa cell cultures (negative)	1	0
Ames test (negative)	2	0
Sister chromatid exchange (negative)	2	0
Alkaline elution test (negative)	1	0
Dominant lethal assay (effect)	1	0
Tissue concentration effects		
Same concentration in placentas and yolk sac	1	0
Placenta higher concentration than fetus	3	0
Less HCB in milk with more children	1	0
Diet determines HCB concentration	1	0
Milk fat HCB constant over time	1	0
Correlation between mother's milk, mother's blood,		
and cord blood	1	0
Transfer HCB from liver to ovary	2	0
High level of HCB (lactation)	1	0
Increase in HCB in breast milk with		
increase in maternal age (linear)	1	0
Mobilization of HCB from fat	1	0
Resorption = higher concentration HCB Fetus and placenta higher concentration at lower dose when exposed later in gestational period than	1	0
those with higher dose in early gestational period	1	0
Higher proportion of HCB in human than rat	1	Ö
Fasting increases concentration in serum	1	0
Higher concentration in male than female serum	1	0
Higher concentration in exposed vs. unexposed Higher transfer of HCB from lactation than from	1	0
placenta	2	0

NOC - not otherwise classified.

Appendix 2. Sample Questionnaire

Follicular Fluid Study (Part II) Pregnancy Outcome

1.	IDENTIFICATION
1.	Name
2.	Identification number
3.	Location: () Hamilton () Halifax () Vancouver
4.	Have you ever had a pregnancy? () YES () NO
	If NO, please proceed to question 7.
	If YES, please continue.

II. PREGNANCY OUTCOME

5. In the table below, please list each of your pregnancies and their outcomes. Begin with your first pregnancy and go in order to your most recent pregnancy.

	Outcome of Pregnancy						
Preg.	Spontan.	Ectopic preg.	Still- birth	Premature birth	Live birth	Multiple birth	Complications of obstetric care
#1							
#2							
#3							
#4							
#5							
#6							

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6.	If you had a live birth or stillbirth, were there any congenital malformations or birth defects?
	() Yes () No
	IF Yes, please specify the type(s) of malformation(s):
III.	ENVIRONMENTAL FACTORS
FAC	IN STUDIES OF PREGNANCY OUTCOME, IT IS CRITICAL TO LUDE INFORMATION ON OTHER IMPORTANT ENVIRONMENTAL TORS SUCH AS SMOKING AND ALCOHOL USE. YOUR RESPONSES IMPORTANT IN THIS INVESTIGATION.
7.	Have you ever smoked?
	() Yes () No — go to question #8
	IF Yes;
	a) At what age did you first smoke?
	b) Do you or did you usually inhale when you smoked? () Yes () No
	c) Did you smoke during your last pregnancy? () Yes () No
	IF Yes;
	 d) How many cigarettes, on average, did you smoke per day? () Less than 1 cigarette per day () 1-10 cigarettes per day () 11-20 cigarettes per day () 20-30 cigarettes per day () > 30 cigarettes per day

8.

9.

10. Have you ever used the following drugs during your last pregnancy?

NEVER SOMETIMES

	a) Cocaine
	b) Hallucinogen (e.g., LSD)
	c) Downers (e.g., sleeping pills)
	d) Uppers (e.g., pep pills)
	e) Heroin or other hard drugs
	f) Marijuana
11.	Did you take any medications, either on the doctor's advice, or by
	buying over-the-counter medication during your last pregnancy?
	() Yes () No () Do not remember
	IF Yes, please check all of the following that apply:
	() vitamins/minerals
	() anti-nausea pills
	() cold remedies
	() allergy preparations
	() laxatives
	() aspirin
	() prescription drugs
	specify:
	() other drugs
	specify:
	Specify.
12.	Before your last pregnancy, what type(s) of drug(s) did you take for fertility treatment?
	() Clomiphene or Clomid [®] or Serophene [®]
	() Bromocriptine
	() Danazol®
	() Progesterone

() $Pergonal^{ ext{ iny B}}$ or hMG — $Human$ $Menopausal$ $Gonadotropin$
() Other
Please specify
13. Has any blood relative had any type of congenital malformation or hereditary disease? (e.g., cystic fibrosis)
() Yes () No
If Yes;
a) please specify the type(s) of malformation(s) or disease(s):
THANK VOILEOD COMPLETING THE OLIECTIONNAIDS IS VOL
THANK YOU FOR COMPLETING THIS QUESTIONNAIRE. IF YOU HAVE ANY FURTHER INFORMATION THAT YOU THINK MAY BE HELPFUL TO US, OR COMMENTS OR QUESTIONS, PLEASE TELL US.

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Pilot Study on Determining the Relative Importance of Risk Factors for Infertility in Canada

Peggy Millson



Abstract

This pilot study was undertaken to determine whether estimates of the relative weighting of risk factors for infertility could be arrived at from the published literature and, where they could not, to recommend potential sources of further information. It was discovered that, although there are few current Canadian data available on many key points, qualitative estimates of the relative magnitude of several risk factors can be provided partly based on data from other developed countries. From these sources, one can conclude that the risk factor of the largest magnitude for which prevention methods are currently known is sexually transmitted diseases, specifically pelvic inflammatory disease caused by chlamydia and gonorrhoea. Substance abuse, in particular tobacco use in women and alcohol use in both sexes, is also likely to be significant because of the widespread use of these substances in the population: however, the degree of increased risk for infertility is less well proven.

There is no doubt that some occupational and environmental exposures are risk factors for infertility; for most such exposures, the information currently available is qualitative and is not sufficient to allow quantitative weighting. Of potential importance but requiring more

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research to quantify the nature and extent of the problem are other substances including marijuana and cocaine; endometriosis; psychological factors including stress; eating disorders; and delayed childbearing.

Executive Summary

This study proposes that the highest priority in infertility prevention be given to the prevention of sexually transmitted diseases (STDs) that lead to pelvic inflammatory disease (PID), particularly chlamydia, because of the evidence of its rising incidence and high rate of asymptomatic infection leading to so-called "silent PID." This is based on evidence of the current impact of STDs as causal factors for infertility, on their preventability, and on compatibility of such prevention with other goals in disease prevention and health promotion (e.g., prevention of human immunodeficiency virus infection).

Fertility decreases with age in all animal species, and in humans it declines in women in their thirties. This should be clearly communicated to the public, since childbearing is increasingly being delayed. Priority needs to be given to addressing social issues that determine whether women can choose not to delay childbearing.

Also a high priority is the development of an effective approach to prevent occupational exposure of women and men to substances suspected of causing adverse reproductive outcomes, while research continues to seek more definitive evidence. Priority should also be given to the prevention and control of substance abuse. From an infertility perspective the most important substance is apparently tobacco; alcohol abuse and use of heroin are other important issues, and the impact of cocaine use is a priority for further research.

Not as high on the priority list for prevention of infertility, but with some role to play nevertheless, is the provision of good contraceptive services. Good counselling is needed for women and men regarding the use of sterilization, to avoid wherever possible later regret and desire for reversal of sterilization, and the inappropriate use of the intrauterine device (IUD), which, although not necessarily a risk for PID in itself, is very likely to increase risk in women who have or may acquire STDs.

There are several risk factors for which evidence is unclear and for which further research is needed to clarify prevention issues. For example, endometriosis would be very important in this regard. Since mild to moderate endometriosis has been determined to be very common, if it were causal in infertility, the resultant population-attributable risk could be quite large. Another example of the need for further research pertains to cocaine use. Since cocaine is probably more widely used in Canada than other illegal drugs (such as heroin), it is important to know if it has significant adverse reproductive impacts for a large number of users. Also worthy of further research is the role of eating disorders and weight problems in infertility. As a starting point, fertility-clinic-based research could be undertaken to document the

prevalence and treatability of these disorders in those seeking care for infertility. Lastly, prospective research into the role of psychological factors and stress in reproduction is also needed. Again, population exposure to these is likely to be widespread. What causes stress differs from person to person. Psychological factors and stress are difficult to study, but elucidation of these aspects is important so that preventive strategies can be considered.

Introduction

Establishing the relative frequency and severity of various risk factors for infertility in the Canadian population is an important initial step in any priority-setting exercise aimed at deciding what resources are needed to tackle the prevention of infertility. Since resources are inevitably limited. such a study could help to direct the most effective resource allocation. Without a systematic effort to establish the relative importance of various identified causes of infertility, there is a risk that important preventable causes of infertility will not receive the attention they deserve. This could lead to resources being focussed on treatment of problems deemed treatable. In turn, this tends to displace attention from the relative costs of this approach versus a prevention-oriented approach, or from attempts to introduce prevention where it could be potentially beneficial.

To examine this issue, it is necessary to first adopt a clear working definition of what constitutes infertility and what the relevant risk factors are. For the purposes of this study, the list of risk factors identified by the Royal Commission's research group has been used as the basis for consideration (see Appendix 1). The definition of infertility is discussed under methodology, but, in general, the study focussed mainly on failure to conceive within one or two years as the measures most frequently available in the literature. Factors affecting either male or female infertility were included wherever relevant.

Subfecundity can be defined to include infertility plus all other involuntary causes of failure to complete a healthy pregnancy, including spontaneous abortion, ectopic pregnancy, and stillbirth. If the weighting of risk factors for infertility has a healthy birth as its relevant end point, then all causes of subfecundity and infertility would ideally be weighted together no matter where they act on the continuum between conception and birth. However, for many risk factors, data may be easier to obtain with respect to their impact in preventing conception versus other aspects of pregnancy. Spontaneous abortion, in particular, is notoriously difficult to quantify because of the high "background rate" that exists in the general population without specific risk factors, and the high rate of spontaneous abortions that may go unrecognized because they occur before the woman

realizes she is pregnant. This study has focussed on failure to conceive as the main outcome for which there are useful data on the impact of risk factors.

Data on infertility generated from treatment services for the infertile suggest that, where a diagnosis can be reached, roughly 40% of infertility in couples is related to female factors alone, about 40% to male factors alone, and about 20% to a combination of male and female factors. Thus, in weighting risk factors for infertility in the general population, risk factors for both male and female infertility are important. Unfortunately, much of the literature on male infertility deals with "poor sperm quality," low sperm counts, et cetera, rather than with underlying risk factors; to some extent this may be true for disturbances of ovulation in women as well. If prevention is to be a priority, more attention must be paid to the search for underlying risk factors in this type of setting.

Another aspect of the picture of infertility obtained from treatment sites is the large proportion of couples for whom no definitive cause of infertility is uncovered, and for whom the diagnosis of "unexplained" or "idiopathic" infertility is applied. This has been reported to range from about 15% to 30% of couples treated. One study has suggested that in some of these unexplained cases the female partner may actually have an eating disorder that goes unrecognized, and that this might be a factor in her infertility. However, given the common occurrence of eating disorders in the population, further study of this relationship would be needed to confirm that this was significantly more common in women with idiopathic infertility. Analogous thinking might lead one to suspect that some cases of unexplained infertility could relate to undiagnosed disorders such as substance abuse, or to unrecognized occupational or environmental exposures. Further research into risk factors for infertility using treatment populations should include a careful consideration of such possible risk factors among the group labelled as having unexplained infertility.

Objectives of the Study

Prior knowledge of the availability of research in this field showed that there would not be sufficient information in the published literature to address relative risk or prevalence in Canada for all risk factors being studied. Therefore, this study was designed as a pilot study, to determine whether estimates could be made of these two factors, relative risk and prevalence, from the published literature for any of the risk factors to be reviewed. Where this was deemed to be feasible, the estimates were developed and are presented with the relevant caveats. Where this was not considered possible, an attempt has been made to suggest alternative sources of information that might enable estimates to be developed. There were two principal objectives:

- 1. To determine the feasibility of obtaining estimates from currently available literature of population-attributable risk (PAR) for each of the major risk factors for infertility as defined by the Royal Commission's research group. Where this was deemed to be feasible, a critical appraisal of the available literature was undertaken, the information available from it was synthesized, and an estimate of PAR was developed. The relative weighting of all estimated risk factors was then considered based on a qualitative assessment of PAR where it could be obtained, as well as on likely feasibility of prevention.
- 2. To consider the feasibility of obtaining further evidence and to provide recommendations for further research for risk factors for which PAR was considered impossible to estimate based on available literature.

Methodology

The approach of this study was to examine the published literature for estimates of how much each risk factor increases the risk of infertility (i.e., relative risk), and for estimates of how prevalent the risk factor under study might be in the population (both male and female, if relevant) of child-bearing age in Canada. Where no Canadian data were available, as was usually the case, data from other industrialized countries were examined to see what estimates might be obtained, how consistent they might be across various countries, and how they might relate to Canada. Table 1 (in "Results" section) provides a summary of the availability of evidence on each of these two measures from published literature. While unpublished literature might provide additional information that would be relevant, and a few related unpublished studies made available by colleagues are included here, the time frame of this study did not permit a full search for unpublished information. Some potential sources are mentioned in connection with research recommendations.

Weighting of Risk Factors

For those risk factors for which it was possible to obtain at least a qualitative estimate of PAR, an attempt was also made to compare risk factors to establish the relative weighting of each within the causation of infertility as a whole. Because reliable Canadian data on which PAR estimates could be based are essentially lacking, the estimates that were attempted should be viewed as suggesting the possible range within which the PAR might lie in order to determine whether a relative weighting could be estimated, and not as firm numerical estimates in their own right. PAR is a measure on a population basis of the impact of the risk factor being

considered, and therefore gives a measure of the potential effect that removal of this factor could have on infertility in the population. This becomes problematic in the situation of infertility where obviously more than one factor may co-exist in the same individual, and no estimates are available to measure the extent of this; furthermore, within a couple, risk factors may co-exist in both partners, and, again, removal of a single factor may not result in successful pregnancy while other factors persist in the other partner.

Use of estimates of prevalence and relative risk from the literature assumes that evidence for the role of these risk factors has been assessed and that bias and confounding in measurement of their frequency and relative risk have been avoided — that is, if an exposure has been erroneously included as a risk factor when it is associated by confounding, "attributable risk" can be calculated, but removal of the risk factor will not,

per se, result in reduction in disease.

Once a ranking of the relative impact of various risk factors on infertility in the population has been completed, other factors need to be considered if the intent is to determine relative priority for intervention to deal with the various factors. These would include:

- 1. Whether exposure to each risk factor can be prevented or controlled by currently available means; whether acceptable and successful means of treatment are available for infertility associated with that particular risk factor (again this depends on the purpose of the priority setting). The judgment about this is likely to include efficiency issues at some point, i.e., the *relative cost* of prevention/treatment for infertility associated with each factor, or even the comparative costs of prevention vs. treatment for some conditions (i.e., cost-effectiveness analysis). It may also include cost-utility considerations, since preferences exist for certain types of outcomes even though they might cost more; for example, prevention might be preferred to treatment because it is inherently more desirable to avoid the stress and uncertainty of treatment.
- 2. Congruence with larger health promotion issues; for example, preventing infertility related to inappropriate leanness, excessive exercise, substance abuse, and even stress might be seen in a more general health promotion context and not as some effort aimed exclusively at preventing infertility.

This study incorporates some discussion of these issues in presenting relative weighting.

Definitions of Infertility

Infertility is defined in a variety of different ways in the literature. As part of the critical appraisal process of each particular study, and to be

able to determine whether results of two or more studies could be reasonably compared, it was necessary to examine the definition used in each of the studies. In general, infertility is defined as either 12 or 24 months or more of unprotected intercourse with failure to conceive. Ideally this definition should also include knowledge that the couple is seeking conception. For some conditions where there is no realistic chance of conception, such as bilateral complete tubal obstruction, hysterectomy, or irreversible azoospermia, these time-dependent definitions are less relevant, and a physician diagnosis alone can be substituted.

Approach to the Published Literature

The first step in the study was a literature search using MEDLINE and TOXLINE data bases. The initial search used as keywords infertility and each of the risk factors to be examined (see Appendix 2 for actual key words used). For many risk factors, this yielded a large number of studies about mechanisms of infertility, treatment, et cetera, that lacked prevalence or risk data. Therefore, a more refined search strategy was adopted using additional terms related to risk (see Appendix 2). The search was limited to literature published in English or French. As discussed below, the search was focussed primarily on the literature published in the past five years (1987-1991 inclusive). The literature raised the issues that follow.

Prevalence Estimates for Risk Factors

In practical terms, only some risk factors are measurable from currently existing literature. Furthermore, published Canadian data are lacking or severely limited for most of the risk factors to be measured, and a decision had to be made about the relevance of data obtained from other countries. This was based on assessment of the comparability of the populations being reported on. Major cultural and social differences precluded use of data from many countries (African countries, for example) as relevant to the Canadian situation. The quality of the actual studies and data sources selected as relevant was also appraised (i.e., their internal validity).

As part of this assessment of the literature, decisions were also required about the time frame of the data to be included. Reporting delays and infrequency of reporting may mean that much of the literature refers to data already a few years old. For the consideration of current and future priorities in the causation of infertility, data pertaining to the past few years can be considered most relevant. In general, the full search strategy was therefore limited to studies published within the past five years; in certain cases older studies were included based on their assessed relevance. Most older studies were identified as key references referred to in more recent

studies; a complete search for literature more than five years old was not undertaken due to time constraints.

The search for relative risk estimates required mainly a careful assessment of the internal validity of the studies from which the estimates were drawn. For this type of data, unless there was reason to expect that relative risk is changing over time, due for example to different treatment of exposures, well-conducted studies of any reasonable vintage that provided a usable estimate of relative risk could be included (i.e., in the absence of more recent evidence or if recent studies were weak, studies more than 10 years old could also be considered). However, once again time constraints resulted in a decision to limit the major search to the past five years and to key references from older identified articles.

Feasibility of Meta-Analysis

If enough studies of reasonable quality exist, then the methods of meta-analysis can be used to mathematically determine a combined estimate of risk based on the estimates from all relevant studies. For the purposes of this study, it was decided that the opportunities for meta-analysis were severely limited by the lack of specific numerical estimates of relative risk for most risk factors, and no attempt was made to conduct such an analysis.

Clustering of Risk Factors

In dealing with both prevalence and relative risk estimation, the problem arises that risk factors may tend to cluster in the same individual or couple, as mentioned above. Since infertility is most simply thought of as an all-or-none phenomenon, it may be that the overlap of factors results in less potential benefit than one might expect from removal of any given risk factor, since other factors that still preclude reproduction may remain. Age may serve as a co-factor to other risk factors, by lowering fertility to some degree in someone who already has somewhat reduced fertility due to other causes, with a combined result of "complete" infertility. Age may also confound other factors; for example, older women may have had more time to suffer repeated episodes of PID, repeated or prolonged occupational hazards, et cetera. Unfortunately, virtually no usable estimates of this overlap issue were found, and weighting of individual risk factors must be regarded as tentative in estimating the potential impact of prevention of individual risk factors until this issue of overlap can be explained through further research.

Infertility Treatment Services as a Source of Data

Data from treatment services for infertility that serve a defined population are a potential source of information about the prevalence of infertility overall, and of infertility potentially linked to various risk factors,

in that population. However, population-based surveys, such as the National Survey of Family Growth (NSFG) in the United States, suggest that in the U.S. population only a portion of those trying unsuccessfully to conceive seek out medical care. It may be that this proportion would be higher in Canada, since universal health insurance should allow access of couples of lower socioeconomic status to such services. This is of some importance, because information from the United States suggests that those seeking treatment for infertility there are disproportionately couples of higher socioeconomic status (Mosher 1988). However, a study from Aberdeen, Scotland, where universal access to health care is also expected, showed a very similar proportion of couples seeking treatment of infertility to that found in the United States (Templeton et al. 1990).

In order to examine the correlation between data from treatment services and population-based data, surveys are needed in Canada that question representative samples of the general population of child-bearing age about their fertility history and their use of infertility treatment services, so that this relationship can be studied. If such studies showed that only a small proportion of the population failed to use such services, they could be relied upon as a principal source of information. However, such information is lacking, and indeed no recently published data of this type from Canadian infertility treatment sources were identified in this study. This is clearly an area where further research could be useful; however, it remains likely that treatment-service-based data will not fully represent the extent of infertility problems in the population. In addition to this issue of representativeness, much of the published information from treatment sources reports physiologic manifestations such as sperm defects or ovulatory abnormalities, without attempting to distinguish various risk factors for these conditions. For these reasons, very little reference is made to literature stemming from treatment sources in this study.

A summary of data availability from the published literature is

presented in Appendix 3.

Results

Overall Prevalence of Infertility in the Canadian Population of Childbearing Age

No general population-based studies were found in the published literature addressing this question for the Canadian population, and the studies the Commission is doing on this will give badly needed information. The U.S. NSFG reported results for 1982 (Mosher 1988) indicating that 2.4 million U.S. couples, constituting 8.5% of all married couples in which the wife was 15-44 years of age, were infertile; 1 million of these (3.5% of total couples) were experiencing primary infertility, i.e., difficulty in conceiving their first child. At the same time, 4.5 million women (8.4% of

all women 15-44) were considered to have impaired fecundity, with 1.9 million of these being childless. The total proportion of infertile couples did not increase over the period 1965-1982 in the United States. However, the proportion of those with primary infertility increased, while those with secondary infertility decreased. The percentage of infertility did increase in one age group, those 20-24 years old. In the subsequent NSFG, carried out in 1988, the proportion of women 15-44 reporting unresolved impaired fecundity was 8.4% (unchanged from 1982), of whom 3.8% had had no live births (primary impaired fecundity) (Mosher and Pratt 1991).

There is reason to believe that the situation in Canada is somewhat similar. A 1984 Canadian fertility survey entitled Family and Childbearing in Canada: A Demographic Analysis (Balakrishnan et al. 1993) has indicated that 8.7% of married women aged 18-49 are noncontraceptively sterile. This is very close to the figure of 8.5% infertility given above, although definitions here may differ, in that the NSFG definition of infertility would not be equivalent to sterility. It is clear that it would be desirable to have population-based estimates of infertility based on representative national sampling similar to the U.S. NSFG for Canada.

Despite the imprecise nature of these overall estimates, they do allow a rough check of the estimates created for individual risk factors. This is helpful in ensuring that none of the latter is incompatible with the probable overall total estimate of infertility in the population.

Risk Estimates for Individual Risk Factors for Infertility

STDs and PID

The most important STDs from the standpoint of infertility are the ones implicated in causation of PID, with its sequelae of tubal damage leading to inability to conceive. Therefore, this study has focussed on gonorrhoea and chlamydia. Both of these STDs are reportable in Canada, but chlamydia became nationally notifiable only in 1990. Furthermore, it is well recognized that there is extensive under-reporting of both these diseases, since they may often be treated without laboratory confirmation, especially in males. Also, many physicians do not report except in conjunction with a positive laboratory test, which is reported directly to public health authorities by the laboratory. The number of cases of undiagnosed and untreated disease is also likely to be substantial, especially for chlamydia, which is believed to have a high rate of asymptomatic infection, even among men. Thus, reported figures for the incidence of both these STDs are clearly underestimates of their prevalence and therefore of their potential to cause PID and infertility.

Reported cases in 1989-1990 in Canada were 50 384 for chlamydia (Gully and Rwetsiba 1991b) and 19 110 for gonorrhoea (Gully and Rwetsiba 1991a). Highest age-specific rates for chlamydia were in young women (16 per 1 000 for ages 15-19 and 15 per 1 000 for ages 20-24). This was also

true for gonorrhoea, at 3.4 per 1 000 for women 15-19 and 2.8 per 1 000 for women 20-24. The United States has produced estimates of diagnosed gonorrhoea and chlamydia infection that try to circumvent under-reporting through active surveillance of cooperating medical care facilities and through projection techniques. This has resulted in an estimate of about 2.01 million cases of chlamydia and 776 200 cases of gonorrhoea in women in the United States annually between 1980 and 1985 (Washington et al. 1987).

If the situation in Canada were roughly comparable, but with about one-tenth the U.S. population, this would produce an estimate of about 201 000 chlamydia cases in women and 77 600 gonorrhoea cases in women treated annually. This is a reasonable assumption, since we are considering only initial disease occurrence here. There is the possibility that more successful contact tracing and treatment in one country would lead to reduced secondary spread, but there is no evidence to indicate that this is the case.

Studies have also been published from Canada, the United States, the United Kingdom, and the Netherlands reporting on chlamydia infection rates obtained from screening asymptomatic sexually active women coming to medical care for other reasons, such as family planning. In most cases, these are women who, because of young age, multiple partners, or other factors, might be considered to be at higher risk for STDs than the overall female population of childbearing age. Prevalence of chlamydia found in these sample populations has ranged from 3.6% to 10.5% overall, and even higher in some age groups. Table 1 summarizes these prevalence studies.

As pointed out by Cates et al. (1990), the relationship of STDs to infertility requires examination of a two-phase temporal lag in effects: from STD to PID, and from PID to infertility. Virtually all PID is related to STDs, since even PID that occurs in persons with IUDs or after abortions or other procedures is commonly caused by chlamydia or gonorrhoea that began as a cervical infection and was then facilitated in reaching the upper genital tract by the presence of an IUD or by introduction of surgical instruments into the uterus.

PID is not reported per se in Canada, although it would be possible to obtain data on the number of women discharged with this diagnosis from hospital discharge data. However, since the majority of cases of PID are likely to be treated without hospitalization, this source would seriously underestimate diagnosed PID. This applies even more to "silent PID," which is believed to be quite common, especially with chlamydia, given the large number of women who present with tubal damage and occlusion attributed to PID, but who do not recall any symptomatic episode of PID in the past.

Table 1. Prevalence of Genital *Chlamydia trachomatis* Infection Reported for Various Populations of Sexually Active Women

Recruitment	Prevalence				
site	Location	Year	(%)*	Reference	
Gynaecology clinic	Helsinki	1978	9	(Paavonen et al. 1978)	
Gynaecology clinic	Boston	1987	4	(Phillips et al. 1987)	
Gynaecology clinic	Indianapolis	1987	9	(Smith et al. 1987)	
Gynaecology clinic (student)	Vancouver	1988	5-8	(Noble et al. 1988)	
Cervical cancer screening program	Amsterdam	1989	4.4 (all aged 35-55)	(Meijer et al. 1989)	
Family planning clinic	Seattle	1986	9	(Handsfield et al. 1986	
Family planning	San Antonio, Texas	1988	10.5	(Glenney et al. 1988)	
Family planning clinic/prenatal clinic	Halmstad, Sweden	1990	15-19 yrs—14% 20-24 yrs—11%	(Ripa 1990)	
Family planning clinic	Hamilton, Ontario	1991	7.2	(Sellors et al. 1991)	
STD clinic	London, England	1976	20	(Oriel et al. 1978)	
STD clinic	Indianapolis	1986	31	(Nettleman et al. 1986	
Family planning/ STD/abortion	Montreal	1991	<25 yrs—11.8% 25-34 yrs—5.7%	(Vincelette et al. 1991	
Abortion	London, England	1983	8	(Ridgway et al. 1983)	
Abortion	Antwerp	1985	12	(Avonts and Piot 1988	
Abortion	Pittsburgh	1986	9	(Amortegul et al. 1986	
Abortion	Quebec City	1987	11.4	(Levallois et al. 1987)	

^{*} Refers to the percentage of the total clinical population screened found to be positive for chlamydia.

Source: Adapted from Fish et al. (1989).

Attempts have been made in the United States, the United Kingdom, and Sweden to quantify the occurrence of PID in the general population. In the United States, an estimate of PID cumulative incidence (equivalent to "prevalence of the post-PID state") was obtained through self-reporting on the NSFG. In this survey, 11% of women of reproductive age reported that they had received treatment for PID, with the proportion reaching 14% among women aged 35-44 (Aral et al. 1991). Since these reports would not include women with asymptomatic PID of which they were unaware, they would tend to underestimate the overall cumulative incidence of PID and hence the potential for subsequent infertility, as well as other effects such as ectopic pregnancy.

The Lund, Sweden, study of PID and infertility produced an estimate that tubal infertility follows PID in women aged 15-34 in 11.4% of those with one episode, 23.1% with two episodes, and 54.3% with three or more episodes of PID (Weström 1980). Their overall estimate for post-salpingitis infertility after one episode in all age groups was 15.2%. Percent infertility because of tubal occlusion after one episode also varied according to severity of the infection: 6.1% for mild infections, 13.4% for moderate, and 30% for severe. This seems to hold true in the case of chlamydial PID

despite antibiotic treatment.

Thus, even if it is assumed that the vast majority of those reporting PID have experienced only one episode, this would mean that a minimum of 15.2% of the 11% reporting past PID, or 1.7% of U.S. women of reproductive age, experience infertility because of previous PID. If we compare this to the reported rate of infertility in the United States of about 8%, this would be about 20% of all infertility in the United States accounted for by tubal occlusion in the female partner due to PID, almost all of which is caused by STDs.

This statistic alone confirms a major role for PID as a cause of reproductive failure. Although a review of ectopic pregnancy is beyond the scope of this study, it may be mentioned that PID has also been estimated to increase the risk of ectopic pregnancy seven- to ten-fold. This results in a ratio of ectopic to intrauterine pregnancy of about 1:16 (Weström 1980) for women in the post-PID state, compared to more than 1:100 under normal conditions. This is a very important factor, because ectopic pregnancy not only represents a failure of successful reproduction but can be life-threatening to the woman involved.

As indicated earlier, these estimates of frequency of PID rely on U.S. and Swedish data and do not offer direct information about the Canadian situation. There is evidence that chlamydia and gonorrhoea are both quite common in Canada, and therefore there is every reason to believe that PID and its sequelae are also common here. Further data are needed to determine how close the estimate produced above for female infertility in the United States is to that in Canada.

In addition to their major effects on female infertility, STDs are known to cause urethritis and epididymitis in males, the latter leading to, at the

least, temporary infertility. There are no data available to quantify the impact these factors may be having on male factor infertility, but there is no doubt that any contribution to male infertility would add to the already

major contribution of STDs to infertility.

Among the other STDs, syphilis can clearly lead to impaired fecundity, mainly through spontaneous abortion and stillbirth caused by congenital syphilis. However, since the reported incidence of congenital syphilis is very low, it was ignored for the purpose of this study. Similarly, an unknown number of sexually transmitted cases of hepatitis B and of human immunodeficiency virus (HIV) infection may lead to a failure of successful pregnancy, mainly through their adverse effects on the health of women. These are not frequent enough to have an appreciable impact on a population-wide basis and have not been included in this study.

Preventability and Treatability

STDs are preventable through primary prevention activities aimed at modifying sexual behaviour, including use of condoms to prevent transmission. PID can also be prevented through successful treatment of genital chlamydial and gonococcal infections. In some cases this would require screening of asymptomatic persons to identify those who are infected but not exhibiting symptoms. Once PID is established, the Lund data suggest that treatment may not be very successful in preventing the progression to infertility. This latter issue needs further study. Once tubal damage has occurred, the damage can be reversed only by successful treatment. At present, treatment is surgical: tubal reconstruction. Alternative treatment involves *in vitro* fertilization (IVF) techniques. These both tend to be relatively difficult and expensive measures, with success by no means assured, if measured with term pregnancy as the outcome.

It is important to note that the age-specific rates reported for chlamydia and gonorrhoea in Canada are currently highest for very young women, most of whom will not yet be attempting to conceive. This may result in an important cohort effect, with high rates of tubal infertility due to these infections being recognized only in the future as these women seek to reproduce.

Delayed Childbearing

There is strong evidence that aging itself causes reduced fertility, independent of the effects of cumulative exposure to other causes of infertility. It probably begins at about age 30, but there is a steeper drop-off after age 35 (Mosher 1988). It is very difficult to quantify this effect with confidence. This is because of internal validity issues in many of the available studies. Some examples are failure to rule out extrinsic causes of infertility not related to age; studies of women undergoing artificial insemination whose chances of becoming pregnant may be lower than with insemination through intercourse; and use of historical data that do not examine frequency of intercourse or occurrence of miscarriage as variables in accounting for decline in births at older ages. However, based on these

studies, a range of relative risk of infertility for older women can be projected. Women over age 35 may be anywhere from 13% to over 50% less fertile than women in their twenties. There is evidence that spontaneous, first-trimester abortion is much more common in older women, especially those over 40 (reported as 10% under age 34; 17.7% aged 35-39; 33.8% aged 40-43; and 53.2% over age 44) (Warburton et al. 1986).

The PAR of infertility associated with age is clearly dependent on the patterns of delayed childbearing occurring in the population. In general, recent demographic trends suggest that women are waiting longer to bear children: average age of first birth, and increased first births to women in their thirties, suggest that more women are likely to be attempting to bear children at older ages. No numeric estimates of these childbearing intentions are really known for the Canadian population, however, so this portion of the estimate is also very difficult to calculate (i.e., the actual number of women "exposed" to seeking to bear children after age 35). An attempt could be made to estimate this based on modelling of trends in ages of childbearing from recent Statistics Canada data. This type of estimate cannot distinguish women with an additional cause for infertility - i.e., those who are seeking to bear children at ages over 35 because they have tried and failed to conceive at a younger age. For such women, primary weighting and primary prevention efforts should first be addressed to their underlying cause of infertility.

Occupational/Environmental Exposures

Both men and women may be exposed to a variety of physical, chemical, and biological hazards in the workplace that could potentially affect their ability to conceive. Because of the huge number of chemical substances to which human beings are exposed both at work and elsewhere, there is a great deal of concern about possible reproductive hazards related to these substances. With the exception of a few substances, however, no proven links exist between individual substances and reproductive failure. Even for substances for which there is general agreement as to their negative impact on fertility or fecundity, it may be necessary to consider whether these effects are reversible or irreversible before deciding on their relative priority among the causes of reproductive impairment; of course, this is true for other risk factors as well as occupational ones.

Hazardous chemical, biological, and physical exposures can potentially cause a whole range of adverse reproductive effects, from failure of spermatogenesis and failure to conceive, through to premature birth or stillbirth. This depends on when in the reproductive process exposure occurs, and the nature of the specific effect. This issue of multiple outcomes, each of which has a background occurrence level that must be measurably exceeded, makes epidemiologic study of any hazard to reproduction difficult. However, in the case of an exposure that may happen to relatively few individuals (as is true for many occupational

exposures), achieving statistically significant evidence of harm may be even more difficult. Thus, the paucity of strong evidence for many risks may reflect in part difficulty in conducting such studies, rather than an actual absence of hazards.

Health and Welfare Canada has recommended that exposure of pregnant workers to the following substances be minimized because of reasonably reliable evidence of adverse effects: ionizing radiation, anaesthetic gases, styrene, ethylene oxide, inorganic lead, inorganic and organic mercury, alcohols, carbon monoxide, dichlorodiphenyltrichloroethane (DDT), 1,2-dibromo-3-chloropropane (DBCP), kepone, diethylstilbestrol (DES), and polychlorinated biphenyls (PCBs) (Canada, Health and Welfare Canada 1987). Most of these would also be considered potentially hazardous to male reproductive function, along with heat exposure to the gonads.

In Ontario, the Ministry of Labour has mandated surveillance and worker protection measures for several specific "designated substances." Some of these, including lead and mercury, have known adverse effects on reproduction, although for some of the substances these effects occur later in the reproductive process and are not necessarily related to infertility per se. No data are currently compiled and published on the numbers of reproductive-age men and women exposed to these substances in the workplace.

In addition to these physical and chemical hazards, several biological agents transmissible in the workplace (e.g., teaching, child-care, and health care workplaces) may have specific adverse effects on reproduction. These include rubella and cytomegalovirus in females — mainly causing fetal damage rather than failure to conceive — and mumps, which may cause orchitis in males, occasionally causing sterility if severe and bilateral.

There are no current estimates in the published literature as to how common exposures to any of the various agents mentioned above might be. Some of this information could probably be made available through Statistics Canada, but data would need to be categorized by sex and age group for examining numbers of reproductive-age women and men potentially exposed and to be compiled with information about the probable nature and extent of exposures in each type of occupation. Even so, use of this information for PAR estimates would still be impossible without reasonable estimates of the relative risks posed by each hazard to be examined.

Thus, for many occupational risks, the information gap is not in acquiring evidence of proven or potential risk of infertility or other reproductive hazard, but in obtaining quantified estimates of the magnitude of this risk, or of the prevalence of exposure to the risk in the Canadian workforce. Until more extensive information becomes available to quantify workplace reproductive hazards, there is even less likelihood of being able to assess the role of the generally much lower levels of potential exposure to reproductive hazards in the general environment. The only exception to this may be accidental environmental exposures of unusual magnitude,

which may have much higher than usual levels of exposure. However, this situation is not representative of the hazards in the general population experiencing only the usual level of exposures.

Contraception

Contraception is obviously practised to avoid reproduction at a time when it is not desired. The important issue is whether some methods have long-term effects — that is, continue to exert a negative influence on the ability to conceive or carry through a healthy pregnancy once this becomes a desired goal. There are several methods of contraception that have been suspected of causing increased risk for later involuntary reproductive failure. The IUD is suspected of causing increased risk of tubal obstruction due to PID. Oral contraceptives cause hormonal changes that sometimes persist after discontinuation of use. Spermicides have been suspected of causing teratogenic effects.

There is no doubt that the methods of voluntary sterilization — tubal ligation in women and vasectomy in men — represent a major barrier to reproduction for those individuals who later decide that they no longer wish to remain sterile and seek reversal of these procedures. Methods of contraception that have only very limited use in the general Canadian population, such as injectable hormones, were not considered here because their overall impact on the Canadian population would be so small.

With respect to the long-term effect of contraception with the IUD, estimates of relative risk in the published literature vary considerably, but it seems reasonable to accept that the main risk is that of sexually transmitted organisms. These may be given an increased opportunity to cause PID by the introduction and/or ongoing presence of an IUD (Huggins and Cullins 1990). Once this has occurred, the woman is at elevated risk for both infertility and ectopic pregnancy, as is any other individual post-PID. The IUD does not appear to cause ectopic pregnancy — it appears that it simply does not protect against it as effectively as other methods in women who are at risk because of tubal damage. Following this line of reasoning, the risks of IUD use could reasonably be incorporated with those of STDs/PID in general, and the risk for those who are not exposed to STDs regarded as apparently minimal (ibid.).

For oral contraception, there is no epidemiologically strong evidence of long-term hormonal effects independent of those caused by other factors (e.g., pre-existing abnormalities, eating disorders, etc.). There is evidence of temporary delay (less than 12 months) in the return to normal fertility in some women (Huggins and Cullins 1990; Vessey et al. 1978). Therefore, use of oral contraception was not given an independent weighting as a risk factor.

With respect to barrier contraception, evidence reviewed dealt with different effects. On the one hand, there seems to be at least moderate evidence that use of barrier contraception, either diaphragm with spermicide or condom with or without spermicide, reduces risk of

acquisition of STDs/PID when compared with those using non-barrier methods. According to some studies, this reduction may be as much as about 50% (Cramer et al. 1987). On the other hand, other studies have suggested the possibility of diminished fertility due to cervical mucous abnormalities (Daling et al. 1987) or teratogenesis/birth defects due to spermicidal chemicals (Jick et al. 1981). Critical review of the evidence for both of these problems suggests that it is quite weak. Therefore, if there is any negative influence on reproductive outcomes due to these forms of contraception, it is likely to be quite small.

There are no data in the literature on the frequency of requests for reversal of either vasectomy or tubal ligation in Canada. Data are also lacking on the proportion of persons seeking donor insemination or IVF to have children after these procedures. This is an important information gap, which should be addressed through further research, since it may assist in the development of practice guidelines about appropriate patient selection and counselling prior to surgical sterilization. Since surgical sterilization has been reported as the most common method of contraception among married Canadian couples (in 1984, 32% of evermarried women and 13% of men had been sterilized [Alderman and Gee 1989], and this may have risen further since that time), desire for restoration of fertility by even a small percentage of these persons could represent a significant factor in infertility treatment. Most of such requests occur in the context of divorce and remarriage, which continue to be common occurrences in Canada.

Endometriosis

Estimation of the PAR for endometriosis as a risk factor for infertility is seriously complicated by the current controversy about whether mild to moderate endometriosis is in any way a causal factor for infertility. At least two recent reviews have attempted to critically assess this controversy (Candiani et al. 1991; Wheeler 1989) and have concluded that there is no convincing evidence that mild to moderate endometriosis is a direct risk factor for infertility. In the case of severe endometriosis accompanied by tubal distortion, it seems reasonable that the endometriosis could cause infertility, but it is also possible that the two simply co-exist because of some other abnormalities. If mild to moderate endometriosis were to be proven to cause infertility, it would be an important risk factor, since the literature suggests that it is very common. One estimate is 2-3% of healthy women in the general population, according to a study from Minnesota (Houston et al. 1987); other reports range up to 10% of the general female population of childbearing age (Wheeler 1989), with 93% of these having only mild or moderate disease. Endometriosis is quite common in fertile as well as infertile women, and hence its role in infertility is unclear.

Substance Abuse

Use of several legal and illegal substances has been implicated in the literature as a potential cause of infertility/subfecundity, including caffeine, alcohol, heroin, cocaine, marijuana, and cigarette smoking. Each of these substances will be considered separately.

- 1. Caffeine: Although there are a few studies suggestive of possible adverse effects of caffeine on delay in conception (Olsen 1991; Wilcox et al. 1988), they differ substantially in the relative risk suggested. They also deal only with delay in conception in women who are in fact all pregnant, so they do not really address the question of the role of caffeine in complete failure to conceive and can by no means be taken as "proof" of adverse effect. There is even less evidence regarding the possibility of adverse pregnancy outcome. If caffeine were to be shown at some future date to have an adverse effect on fertility or pregnancy outcome, its widespread use would mean that its PAR could be substantial. Because of the unproven nature of this suggestion, caffeine was not given a weighting in this study.
- Alcohol: Although chronic alcoholism in women may cause some 2. disruption of menstrual patterns (Becker et al. 1989), there is no evidence that this has any significant effect in reducing fertility. In itself, this is not unexpected, since a completely regular menstrual pattern is not required for pregnancy. There is strong evidence that heavy alcohol intake, and perhaps even moderate intake, during pregnancy has important adverse effects on the fetus (fetal alcohol syndrome). This is likely to represent the most important reproductive risk attributable to alcohol. In addition, there is evidence that chronic alcoholism can damage male fertility, with effects such as impotence and testicular atrophy. However, the exact level of alcohol intake (amount and/or duration) required to produce the effects is not fully defined. It may be that levels of intake that impair sexual performance to a degree less than complete impotence could still adversely affect reproduction, but this has not been documented in the literature.

It has been estimated by the Addiction Research Foundation that in 1988 about 477 000 Canadian adults, or 3% of the adult population, were alcoholics; about 70% of these were men. It is unknown how many of these men would be infertile due to their alcoholism. If it were around 10%, this would constitute about 31 000 men; if it were 1%, it would be 3 100. Thus, the effect of alcohol abuse on fertility is not clear. As context, there were 391 925 live births reported in Canada in 1989.

3. Heroin: It has been reported that up to 90% of female heroin addicts experience menstrual abnormalities while abusing heroin, with 63% of active users in the same study experiencing infertility (Stoffer 1968). A study of sexual problems in male heroin addicts indicated that 15%

were impotent while using drugs, and a further 28% were sometimes impotent (Mintz et al. 1974). The exact number of heroin addicts in Canada is unknown, but it is estimated to be several thousand. If it is assumed that most of these individuals are of childbearing age, and that the above proportions are infertile, this would constitute several thousand infertile individuals in the population. It would be expected that much of this infertility would be reversible with successful treatment of the addiction.

4. Cocaine: At least one recent study has reported abnormalities in the sperm of men attending an infertility clinic, correlated with cocaine use (Bracken et al. 1990). However, these men had also used several other drugs, and the exact relationship of cocaine to fertility, as opposed to abnormalities of semen analysis alone, is not known. There does not appear to be any good risk estimate on which to base an assessment of the impact of cocaine on male infertility in the population. Also, although adverse outcomes of cocaine use in pregnancy have been reported in the literature, including infarction of cerebral blood vessels of the fetus and effects of addiction in the newborn, there are no data on which to base an estimate of the degree of risk involved with respect to such outcomes.

The National Alcohol and Other Drugs Survey in 1989 found that 1.4% of Canadian adults (280 000 persons) had used cocaine (Canada, Health and Welfare Canada 1991). Its effects are likely to be reversible over time. Further research into its reproductive effects would seem to be an important requirement.

- 5. Marijuana (Cannabis): The same survey of drug use found that 6.5% of Canadian adults reported cannabis use in the previous year. However, there is as yet no strong evidence linking marijuana use to infertility or adverse pregnancy outcomes, despite suggestive evidence of semen abnormalities in regular users (Close et al. 1990). Thus, although it is considered prudent to advise persons seeking pregnancy to refrain from marijuana use, the lack of evidence to quantify a risk, if one exists, resulted in a decision not to weight this factor for this study.
- 6. Cigarette Smoking: Cigarette smoking is implicated in reduced female fertility, although it is difficult to separate the effects of other accompanying risks. If an independent risk for cigarette smoking does exist, it may be estimated to be in the order of a relative risk of 1.5-2 (Howe et al. 1985; Olsen et al. 1983). Over 30% of the adult Canadian female population currently smoke. Thus, the PAR for cigarette smoking with respect to female infertility might be in the order of

14-24%.* In addition, there is also a well-recognized effect in reducing birthweight. Cigarette smoking in women is of particular concern because there has been a recent pattern of increasing use of cigarettes among young women, which could make this a risk factor that will increase in the future.

Eating Disorders/Exercise

These risk factors are potentially important for female fertility, while they have not been shown to affect male fertility. It is estimated that as much as 1% of the adolescent and young adult female population suffers from anorexia nervosa (Garfinkel and Garner 1982), and many if not most of these women, particularly those who become severely underweight, will suffer from menstrual disorders and amenorrhoea, with a reported fertility rate of about one-third the expected (Brinch et al. 1988). In addition, a further 1.7% of young women are reported to have bulimia, and perhaps 3-4% have less specific eating disorders (Stewart et al. 1990).

These women are less likely to have the extreme weight loss and menstrual disruptions of anorexics, but one source suggests that up to 50% of bulimics experience menstrual disorders (Pirke et al. 1987). However, many young women with eating disorders will not yet be seeking to become pregnant, and since their condition is generally reversible they may be restored to relatively normal fertility if their eating disorder is resolved. While suffering from eating disorder, the risk of infertility is substantial; furthermore, some studies of "unexplained infertility" in infertility clinics have suggested that eating disorders may be an important cause of infertility in such patients (Bates 1985). Therefore, it could be estimated that about 1-2% of young women may suffer from infertility related to eating disorders, which at least are potentially reversible if treated.

Studies of athletes show that menstrual disturbances and amenorrhoea may occur in women who engage in strenuous exercise, particularly if this is accompanied by a loss of body fat to relatively low levels (Highet 1989). This condition, too, is reversible if body weight is allowed to approach normal levels. No prevalence data are available from the literature consulted to indicate how widespread this problem may be.

Obesity has also been of potential concern with respect to infertility. However, most obese women and men are fertile, and no clear causal link has been established between obesity and male or female infertility. This issue may require further research.

^{*} This was calculated as follows: (Prevalence of exposure) × (Rate ratio – 1)

1 + [(Prevalence of exposure) × (Rate ratio – 1)]

Using a rate ratio of 1.5 and prevalence of 32%, this yields 13.8%; using a rate ratio of 2.0, this yields 24.2%.

Medical/Surgical Factors

A variety of medical and surgical conditions and treatments may have an impact on fertility. Several of these are discussed below.

Therapeutic abortion: The literature suggests there is no increased risk of infertility in women who have undergone a single therapeutic abortion (Hogue et al. 1982; Huggins and Cullins 1990), provided they do not contract PID. This may occur as a result of the introduction into the upper genital tract during surgery of a pre-existing chlamydial or gonorrhoeal cervical infection. It is now widespread practice to screen women seeking termination of pregnancy for STDs and to treat them to prevent such serious infectious sequelae.

There is also some concern about the possibility that women undergoing repeated therapeutic abortion may be at increased risk for subsequent infertility. To date there is insufficient evidence to draw a clear conclusion (Huggins and Cullins 1990). The effects may be rather hard to sort out from the effects of elevated STD rates or other factors in these women.

Treatment of genital tract cancers: Hysterectomy for cervical or other cancers will obviously terminate the fertility of the women involved. Despite the large number of cervical abnormalities detected through Pap smears, hysterectomy in women of childbearing age is a relatively uncommon outcome and would have little impact on population figures for infertility. Effective prevention of STDs in women could also have benefits in reduced incidence of papillomavirus infection, which is a risk factor for cervical cancer and hence in these sequelae of treatment.

Treatment of male testicular cancers with surgery or radiation may result in temporary or permanent infertility (Peckham 1988). Even if bilateral removal of testes is needed, the relative rarity of these cases makes the fertility impact of treatment for this and other cancers in young people very small. No further attempt was made to weight this particular factor.

Psychological Factors

A recent review indicates that psychological abnormalities are much more common in infertile couples than in a control group of couples who are not suffering from infertility. However, most research does not establish the sequence of events; it does not distinguish between stress and psychological problems as causes of infertility and their role as outcomes of infertility and of the investigation and treatment process (Wright et al. 1989). It is very difficult to establish population-based estimates of the frequency and severity of stress that are useful for potentially determining the PAR of psychological factors as risk factors for infertility. If psychological factors do play a role as risk factors for infertility, presumably they would be related to at least some of the cases labelled as "unexplained" infertility in infertility treatment centres. In some series, about a quarter of the total cases seen for treatment are of unexplained origin.

Conclusion — Relative Weighting of Risk Factors for Infertility

This study set out to document the feasibility of weighting risk factors for infertility. We conclude that, although there are no definitive measurements available for Canada from the literature for any of the risk factors under discussion, it is possible to at least estimate the likely order of magnitude for some factors. Thus, a qualitative relative weighting can be estimated on the basis of available information for some of the risk factors. If the weighting is to be useful for priority setting among risk factors, at least from a public health perspective, the issues of preventability and reversibility should also be examined, and judgments

about them incorporated into the suggested weighting.

Among the risk factors examined, prevention and control strategies are available or can be developed using current knowledge for STDs, delayed childbearing, some particular occupational and environmental exposures, patterns of contraceptive use, substance abuse, eating disorders and exercise, and psychological factors and stress. Of these, the factor with the strongest evidence for a significant PAR as a causal factor for infertility is STDs. There is strong evidence regarding some subsets of occupational and environmental exposure and substance abuse. However, for occupational and environmental exposure to substances known to cause infertility, the PAR can only be guessed at until more information is provided about the extent of exposure of persons of childbearing age in the population.

Heroin addiction in both sexes and chronic alcoholism in men are very likely to cause a serious and in many cases irreversible effect on fertility. However, the number of people exposed during the years in which they seek to reproduce is not fully documented. It is unclear what proportion they make up of those wishing to have children. The possible relative risks for some of the other substances are not very large (e.g., about 1.5) and may be somewhat controversial, but, for cigarette smoking in particular, the widespread exposure to these risks in the population (because of continuing high rates of smoking among young women, for example) is likely to mean these substances have a much greater potential PAR. With respect to cigarette smoking, programs aimed at reducing smoking among young people are already ongoing, so prevention is feasible through a number of strategies and would have other benefits resulting from reduced smoking in the population.

Eating disorders and exercise, although common, might be regarded as of lower priority from the point of view of prevention of infertility, since once recognized they are potentially reversible. Their prevention is linked to many broader social issues related to the image and role of women, which require prevention programs aimed well beyond infertility alone.

Although the effect of delayed childbearing is difficult to quantify, there is general agreement that fertility does decline with age; prevention of this risk would require social policies aimed at facilitating the choice to bear children at more biologically appropriate ages.

Appendix 4 summarizes the qualitative weighting for all the infertility

risk factors examined.

Recommendations

Research Required to Establish Risk and Direct Prevention

1. Occupational and environmental hazards: A separate research project should be undertaken to bring together unpublished sources and a more complete literature overview (including older literature) for known and suspected hazards as they relate to infertility. This would ideally be part of a larger study incorporating other forms of reproductive failure (i.e., spontaneous abortion, congenital abnormality, etc.). This research should include compiling information on the number of workers (male and female) of childbearing age currently exposed to these risks in Canada.

However, where reproductive hazard is already established or strongly suspected, prevention could be strongly recommended even

without these data.

- 2. Substance abuse: There is an urgent need to determine the risk of reproductive hazard related to cocaine and marijuana use, in particular that related to preconceptual and early pregnancy (prior to recognition of pregnancy), and the level of exposure to these substances required for them to be hazardous, since many persons use them intermittently rather than chronically (once this is established, some Canadian estimates of prevalence of use of these substances are already available from other surveys).
- 3. Psychological factors/stress: Although stress is a common issue in Canadian society, the risk for infertility associated with it is not established, and this is an important research priority. To examine stress and other psychological factors as risk factors preceding evidence of infertility, and to avoid confounding by the effect of infertility itself in inducing stress and other psychological problems, it is essential that such research be prospective. Depending on the outcome of this risk-related research, it might then be necessary to document prevalence of relevant psychological factors. On the other hand, it might be reasonable to recommend preventive action related to common psychological problems without specific prevalence research.

- 4. Reversal of surgical sterilization: Information should be sought from Hospital Medical Records Institute (HMRI) data, provincial health insurance plan records, or providers of tubal reconstructive surgery if need be, to document the prevalence of requests and/or actual procedures for reversal of previous surgical sterilization, by age and sex of the patient. If this is found to be a relatively common occurrence, then specific epidemiologic studies should be undertaken to characterize in more detail who is requesting reversal, what their reproductive history has been (including when and why they were sterilized), and why they are now requesting reversal, as well as the subsequent reproductive outcome. From this information prevention strategies could be developed if indicated.
- 5. Delayed childbearing: There is strong evidence that fertility declines with age, although estimates of the exact degree of decline vary. With the trend toward older ages of childbearing apparent in recent Canadian birth data, there is reason to be concerned about this risk for infertility, even though its exact extent is not fully documented. Research on prevention of this risk would need to focus on social factors leading women to delay childbearing, and means to overcome these through alteration of incentives and elimination of barriers to women in beginning childbearing earlier.

Appendix 1. Risk Factors for Infertility Examined in This Study

Sexually transmitted diseases

Delayed childbearing

Occupational and environmental exposures

Endometriosis

Substance abuse

Weight/exercise

Contraception

Medical/surgical conditions

Psychological factors/stress

Appendix 2. Search Strategies Used for MEDLINE Searches

The following are the key words and search instructions used for the search for prevalence information and relative risk information for the risk factors examined in this study.

Sexually Transmitted Diseases:

(((INFERTIL*[ALL] AND ((("SEXUALLYTRANSMITTED DISEASE*"[ALL] OR ADNEXITIS[ALL] OR GONORRHEA[ALL] OR CHLAMYDIA[ALL]))) AND (((RISK[ALL] OR "ODDS RATIO"[ALL] OR PREVALENCE[ALL])

Occupational/Environmental Exposures:

(((INFERTIL*[ALL]) AND (((OCCUPATIONAL[ALL] OR ENVIRONMENTAL[ALL] OR "HAZARDOUS SUBSTANCE*"[ALL] OR RADIATION[ALL]))) AND ((((RISK[ALL] OR "ODDS RATIO"[ALL] OR PREVALENCE[ALL]))

Endometriosis:

(((INFERTIL*[ALL] AND (ENDOMETRIOSIS[ALL]))) AND ((((RISK[ALL] OR "ODDS RATIO"[ALL]) OR PREVALENCE[ALL]))

Substance Abuse:

(((INFERTIL*[ALL]) AND (SMOKING[ALL] OR "TOBACCO SMOKE POLLUTION"[ALL]))) AND ((((RISK[ALL]) OR "ODDS RATIO"[ALL] OR PREVALENCE[ALL]))

(((INFERTIL*[ALL] AND (((("SUBSTANCE ABUSE"[ALL] OR "SUBSTANCE DEPENDENCE"[ALL]) OR "SUBSTANCE DEPENDENCE"[ALL] OR "SUBSTANCE USE DISORDERS"[ALL] OR ALCOHOLI*[ALL]))) AND (((RISK[ALL]) OR "ODDS RATIO"[ALL] OR PREVALENCE[ALL])

Weight/Exercise:

(((INFERTIL*[ALL] AND ((((("EATING DISORDER*"[ALL] OR ANOREXIA[ALL]) OR BULIMIA[ALL] OR OBESITY[ALL] OR "EXERCISE"[ALL]))) AND ((((RISK[ALL] OR "ODDS RATIO"[ALL] OR PREVALENCE[ALL]))

Contraception:

(((INFERTIL*[ALL]) AND ((CONTRACEPTI*[ALL] OR "INTRAUTERINE DEVICE*"[ALL]) OR STERILIZATION[ALL]))) AND ((((RISK[ALL] OR "ODDS RATIO"[ALL] OR PREVALENCE[ALL])))

Medical/Surgical Conditions:

(((INFERTIL*[ALL] AND ("IATROGENIC"[ALL]))) AND ((((RISK[ALL]) OR "ODDS RATIO"[ALL] OR PREVALENCE[ALL]))

Psychological Factors/Stress:

(((INFERTIL*[ALL]) AND ((PSYCHOLOGIC[ALL] OR STRESS[ALL]) OR PSYCHOLOGIC*[ALL]))) AND ((((RISK[ALL] OR "ODDS RATIO"[ALL] OR PREVALENCE[ALL]))

Delayed Childbearing:

(((INFERTIL*[ALL]) AND (((AGING[ALL] OR "AGE FACTORS"[ALL]) OR "PATERNAL AGE"[ALL] OR "MATERNAL AGE"[ALL]))) AND ((((RISK[ALL]) OR "ODDS RATIO"[ALL] OR PREVALENCE[ALL]))

Appendix 3. Summary of Data Availability from Published Literature for Estimation of Population-Attributable Risk for Infertility Risk Factors

Table 3A. Summary of Data Availability from Published Literature for Estimation of Population-Attributable Risk for Infertility Risk Factors

Risk factor	Relative risk for infertility	Prevalence estimate for Canadian, or reasonable substitute, population
Sexually transmitted diseases	+	+
Occupational and environmental	+/- (limited availability)	-
Endometriosis	– (due to scientific uncertainty)	+
Substance abuse:		
a. caffeine	-	- (common)
b. alcohol	-	+
c. heroin d. cocaine	+	-
		+
e. marijuana f. cigarettes	+	+
i. cigarettes	T	T
Weight/exercise	-	+
Contraception:		
a. oral	+	+
b. IUD	+	+
c. barrier	+	+
d. sterilization	+	+ (but prevalence of reversal requests unknown)
Medical/surgical conditions		
a. induced abortion	+	+
b. cancer treatment	+	_

Risk factor	Relative risk for infertility	Prevalence estimate for Canadian, or reasonable substitute, population	
Psychological/stress	_	-	
Aging (delayed childbearing)	+/- (some scientific uncertainty)	+/- (some evidence but no overall estimates)	

Appendix 4. Summary of Qualitative Weighting for All Infertility Risk Factors Examined

High Priorities for Prevention Programs

1. Factors with strong evidence of risk, known high prevalence, and available prevention:

PID due to chlamydia and gonorrhoea

2. Factors with strong evidence of risk, moderately high prevalence, and available prevention or treatment:

Substance abuse: alcohol (males) heroin (both sexes)

3. Factors with strong evidence of risk and available prevention requiring more information on prevalence:

Occupational exposures, including radiation and heat, toxins such as lead and DBCP, and, more rarely, biological hazards, e.g., mumps

Intermediate Priorities for Prevention Programs

1. Factors with weaker, more controversial risk estimates, high prevalence, and available prevention:

Substance abuse: smoking Weight/exercise

Aging (prevention would refer to increased public awareness and social policies to shift late childbearing to somewhat younger ages)

Research Priorities

 Factors with high prevalence requiring more evidence to determine risk:

Substance Abuse: cocaine
marijuana
Endometriosis (especially mild/moderate)
Psychological factors/stress

2. Factors with high risk, unknown prevalence:

Medical/surgical: reversal of surgical sterilization

Some occupational and environmental risks are also research priorities because their relative risk is not well known, or their prevalence needs to be documented in order to target prevention.

Low Priorities

1. Factors with probably low risk:

Contraception (except IUD use in those at risk for PID from STDs) Medical/surgical: abortion

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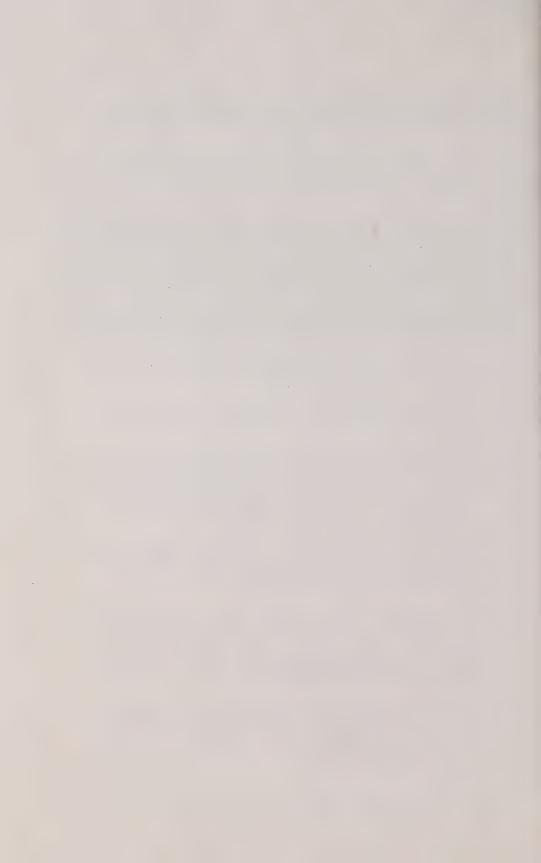
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Mandate

(approved by Her Excellency the Governor General on the 25th day of October, 1989)

The Committee of the Privy Council, on the recommendation of the Prime Minister, advise that a Commission do issue under Part I of the Inquiries Act and under the Great Seal of Canada appointing The Royal Commission on New Reproductive Technologies to inquire into and report on current and potential medical and scientific developments related to new reproductive technologies, considering in particular their social, ethical, health, research, legal and economic implications and the public interest, recommending what policies and safeguards should be applied, and examining in particular,

- (a) implications of new reproductive technologies for women's reproductive health and well-being;
- (b) the causes, treatment and prevention of male and female infertility;
- (c) reversals of sterilization procedures, artificial insemination, in vitro fertilization, embryo transfers, prenatal screening and diagnostic techniques, genetic manipulation and therapeutic interventions to correct genetic anomalies, sex selection techniques, embryo experimentation and fetal tissue transplants;
- social and legal arrangements, such as surrogate childbearing, judicial interventions during gestation and birth, and "ownership" of ova, sperm, embryos and fetal tissue;
- (e) the status and rights of people using or contributing to reproductive services, such as access to procedures, "rights" to parenthood, informed consent, status of gamete donors and confidentiality, and the impact of these services on all concerned parties, particularly the children; and
- (f) the economic ramifications of these technologies, such as the commercial marketing of ova, sperm and embryos, the application of patent law, and the funding of research and procedures including infertility treatment.



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